UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

February 21, 2006

SUBJECT: **Piperonyl Butoxide** HED Revised Risk Assessment for Reregistration Eligibility Document (RED) PC Code No 067501; DP Barcode No. 326576

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Attached is Health Effects Division's (HED's) risk assessment of piperonyl butoxide for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This document updates the September 8, 2005 Piperonyl Butoxide HED Risk Assessment. The risk assessment has been revised to address public comments. The revised disciplinary science chapters and other supporting documents are included as appendices as follows:

Report of the Hazard Identification Assessment Review Committee, S. Ramasamy (TXR No.0052600, 6/8/04) (Note: This is an archive data base document which cannot be revised. Revisions to the toxicology assessment have been addressed in the Risk Assessment)
Report of the Metabolism Assessment Review Committee, T Morton, S. Ramasamy, W. Eckel (D321269, 9/1/05)
Product & Residue Chemistry Assessment, T. Morton (D310030, 11/23/04)
Occupational and Residential Exposure Assessment, B. Daiss (D318743, 9/7/05),
Occupational and Residential Exposure Assessment for the Use of Piperonyl Butoxide in Residential Outdoor Automatic Mister Systems, M. Crowley (D315334, 8/30/05)
Dietary Exposure and Risk Estimates for Tolerance Reassessment, T. Morton (D310032, 11/23/04)
Review of Pyrethrins Incident Reports - Second Revision, J. Blondell, Ph.D (D320300, 8/16/04)
Tier I Drinking Water Assessment, William Eckel (D286223, 5/17/04)

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1.0 EXECUTIVE SUMMARY

This assessment provides information to support the issuance of a risk management decision document known as a Reregistration Eligibility Decision (RED) Document for piperonyl butoxide. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Piperonyl butoxide is an insecticide synergist. Synergists are chemicals that lack pesticidal effects of their own but enhance the pesticidal properties of other chemicals. Piperonyl butoxide is used in combination with a wide variety of insecticides in ratios ranging from 3:1 to 20:1 by weight. It is usually formulated with natural pyrethrins or synthetic pyrethroids and is an ingredient in 1600 to 1700 registered pest control products. It has numerous and varied commercial and residential applications, is available in a broad range of formulations, and is applied by wide variety of application methods. Commercial uses include pre- and post-harvest application to food and non-food agricultural crops, applications in food and non-food handling commercial and agricultural structures and outdoor premises, housing for veterinary and farm animals, and direct application to veterinary and farm animals. Piperonyl butoxide currently has 70 tolerances (40 CFR 180.127) in/on various crop and livestock food commodities. Residentially, it is used to control insects both inside the home, and outside on gardens, lawns and ornamentals, patios, and other outdoor structures, and is directly applied to pets. As a synergist, it inhibits the mixed function oxidase system of insects and reduces the oxidative breakdown of other pesticides like pyrethrum and synthetic pyrethroids. Comprehensive information on use patterns and formulations is provided in the Piperonyl Butoxide Master Label which was submitted to the EPA by the Piperonyl Butoxide Task Force II. The risk assessments for piperonyl butoxide are based solely on the Master Label, since it only lists the uses that the Task Force II are supporting (C. Rodia, Use Closure Memo, 11/17/03).

Screening level estimate of piperonyl butoxide usage performed by HED's Biological and Economical Analysis Division (BEAD) indicates that 5,000 to 10,000 pounds of piperonyl butoxide are used annually in the U.S. for application to agricultural crops, with highest usage on potatoes (30% crop treated) and other uses at 5% or less. An estimated 100,000 to 200,000 pounds are used annually for non-crop uses.

Regulatory History

Piperonyl butoxide is a FIFRA List B reregistration pesticide. The Phase 4 Reviews of available residue chemistry data were issued in February, 1991. Data-Call-In Notices for piperonyl butoxide were issued in May, 1991 and September, 1995 requiring the registrants to submit several residue chemistry studies in order to fulfill reregistration requirements. Reregistration of piperonyl butoxide is being supported by the Piperonyl Butoxide Task Force II, whose members are Prentiss, Inc., McLaughlin Gormley King Co., S.C. Johnson & Son, Inc., Takasago International Corp., Endura S.p.A., and Valent Biosciences Corp. Data has been submitted in response to data deficiencies outlined in the Phase 4 Reviews; to date, all studies have been reviewed.

Hazard Identification and Dose Response Assessment

The toxicology data base is adequate to characterize the toxicity of piperonyl butoxide. Piperonyl butoxide has a low acute toxicity by oral, inhalation and dermal routes and it has been assigned toxicity Category IV by all exposure routes. In the acute studies, piperonyl butoxide has been identified as minimally irritating to eyes and skin.

The liver is primary target organ for piperonyl butoxide induced toxicity. Subchronic studies in rats showed increases in liver weight, increases in cholesterol and gamma glutamyl transpeptidase activity, and histopathological effects such as enlargement of hepatocytes, oval cell proliferation, bile duct hyperplasia, and focal necrosis. Similar effects occurred in subchronic mice study after 20 days. The liver effects (increased liver weight, focal hyperplasia and changes in clinical parameters) appeared pronounced upon chronic exposure to piperonyl butoxide in rodents and dogs.

In a subchronic dermal toxicity study in rabbits, no systemic treatment related effects were observed. However, piperonyl butoxide was observed to be a mild irritant i.e., macro and micropathology of the tested sites exhibited dermal lesions associated with irritation. A subchronic inhalation toxicity study in rats showed histopathological changes in the respiratory tract indicated by metaplasia/ hyperplasia in the larynx in all treated groups.

In a combined chronic/carcinogenic study in rats, positive carcinogenic effects were reported at doses where high incidence of ileocaecal ulcers were noticed. Liver adenomas and carcinomas were reported in Fischer 344 rats only when tested at excessive doses. A slight increase in thyroid follicular cell tumor alone was reported in Sprague Dawley rats when tested at adequate doses. A 1979 National Toxicology Program (NTP) study reported negative effects for carcinogenicity in same strain of rats and in B6C3F1 mice. However, in CD-1 mice, piperonyl butoxide tested positive for liver tumor effects. Piperonyl butoxide is classified as a Group C-possible human carcinogen with no cancer quantification required for piperonyl butoxide risk assessment.

The toxicity database is considered adequate for evaluation of risks to infants and children. Studies indicate that there is a low degree of concern for fetal susceptibility effects and no

evidence of residual uncertainties for pre- and post-natal toxicity from exposure to piperonyl butoxide. No developmental toxic effects were noted in guideline studies in rats and rabbits. Neurotoxic effects are not evident from the clinical signs reported in guideline developmental, reproductive and chronic studies. Therefore, the special FQPA safety factor is reduced from 10x to 1x.

Piperonyl butoxide tested negative in bacterial gene mutation assays. The *in vitro* mammalian cell mutation assays indicate a questionable positive effect for mutation. Piperonyl butoxide tested negative for chromosomal aberration and sister chromatid exchange in CHO cells and no induction of unscheduled DNA synthesis was observed in rat primary hepatocytes.

Piperonyl butoxide is well known to inhibit microsomal enzymes in insects. It also inhibits the microsomal enzymes in several other species (e.g., rats, rabbits, mice). In the mammalian system, it is shown to exhibit initial inhibition followed by stimulation of microsomal enzymes upon continued exposure. The kinetics of piperonyl butoxide inhibition and/or stimulation of microsomal enzymes in humans is not established. However, one study in humans reports no inhibition of microsomal enzymes (measured as antipyrine half-life in blood) at a dose of 0.7 mg/kg.

Metabolism studies show the main route of piperonyl butoxide excretion in rats is via urine and feces (64-85% in feces, 11-30% in urine) with the majority of the radioactivity being excreted within 48 hours. The parent and the M3 metabolite (parent with opened methylene dioxy ring) were the major compounds identified in feces (approximately 20% of the radioactivity each).

Dietary, drinking water, and occupational and residential exposure scenarios are the relevant scenarios for exposure to piperonyl butoxide. The acute oral endpoint was selected based on a developmental toxicity study in rats. The chronic oral endpoint was selected based on a chronic oral toxicity study in dogs. No dose or endpoints were selected for dermal exposure because no systemic effects were observed at the limit dose in the 21-day dermal toxicity study in rabbits. The short-, intermediate-term and long-term inhalation endpoints were selected based on a subchronic inhalation study in rats. Short and intermediate term incidental oral endpoints were selected based on a two generation reproduction study in rats. Endpoints used in the assessment are provided in Table 1.

Table 1. Endpoints Used for Piperonyl Butoxide Risk Assessment

Dietary	NOAEL mg/kg/day	RfD mg/kg/day	PAD mg/kg/day
acute - all populations	630	6.3 (UF=100; FQPA = 1)	6.3
chronic - all populations	15.5	0.155 (UF=100; FQPA = 1)	0.155
Occupational and Residential	NOAEL mg/kg/day	MOE	
short intermediate & long-term dermal	NA	NA	
short-term incidental oral	89	100	

Table 1. Endpoints Used for Piperonyl Butoxide Risk Assessment		
short & intermediate-term inhalation	4	300
long-term inhalation	4	1000

Exposure Assessment

Analysis of dietary, drinking water, occupational and residential exposure pathways were included in the piperonyl butoxide risk assessment. Sources of dietary exposure include pre- and post harvest food crops, livestock, and food from treated food processing facilities and food storage warehouses. Drinking water exposure may occur due to run-off from agricultural use, outdoor pest control, mosquito abatement and some direct aquatic uses (e.g., carp bait). Occupational exposure may occur through use of piperonyl butoxide during application for agricultural, commercial and residential pest control, and mosquito abatement activities. Residential exposures may occur through homeowner use of piperonyl butoxide to control pests indoors, outdoors and on pets. For the occupational exposures, short-, intermediate-, and long term inhalation pathways were assessed based on label directed use patterns. For residential exposures, short- and intermediate-term inhalation and incidental oral pathways were assessed. Dermal exposures were not assessed because HIARC concluded that no quantitative dermal assessment is required because no systemic effects were observed at high doses in dermal toxicity studies.

Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary, drinking water, residential and occupational exposure pathways. An aggregate assessment of risk from the combined food and drinking water pathways was also conducted. Oral and inhalation residential exposures to piperonyl butoxide were not aggregated because the toxicity endpoints selected for these routes of exposure are not common. A cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity has not been conducted for this RED because HED has not yet determined if there are any other chemical substances that have a mechanism of toxicity common with that of piperonyl butoxide.

Food Pathway Exposure and Risk

HED conducted highly refined acute and chronic dietary exposure analyses using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™) and the Lifeline model. Dietary analyses were conducted for the general U.S. population and all population subgroups.

Acute and chronic dietary risks are expressed as a percentage of the acute or chronic Population Adjusted Dose (aPAD or cPAD). A dietary risk of 100% of the PAD is the target level of exposure that should not be exceeded, (i.e., estimated risk less than 100% of PAD is not of concern). The PAD is the Acute reference dose (RfD) or the Chronic RfD modified by the FQPA Safety Factor. The safety factor for both the acute and chronic dietary assessments is 1X.

Based on these analyses, acute and chronic dietary risk from existing and proposed uses of piperonyl butoxide are below HED's level of concern for the general US population and population subgroups. The 99.9th percentile acute exposure estimates were < 100% of the aPAD. The highest acute exposures (1.2 mg/kg/day) were in children 1-2 years old (20% aPAD). Chronic exposure estimates were also <100% of the cPAD, with the highest chronic exposure (0.02 mg/kg/day) occurring in children 1-2 years old (12% cPAD).

Drinking Water Pathway Exposure and Risk

The Environmental Fate and Effects Division (EFED) performed a Tier I drinking water assessment for piperonyl butoxide in surface water and groundwater (D286223, W. Eckel, 5/17/04). EFED used the FIRST (FQPA Index Reservoir Screening Tool) model for estimating the upper bound on the concentrations that could occur in surface-water-source drinking water, and SCIGROW (Screening Concentration in Ground Water) to estimate the concentrations in groundwater used for drinking water. The peak estimated drinking water concentration (EDWC) of piperonyl butoxide in surface water is 240 ppb. The annual average drinking water EDWC in surface water is 60 ppb. The peak and annual average groundwater EDWCs are 0.26 ppb.

Aggregate Exposures and Risks

Since there is potential for concurrent exposure via food and water, the combined exposures are estimated for the aggregate assessment. To assess aggregate risk, drinking water levels of comparison (DWLOCs) are compared with model-based EDWCs determined by EFED. The DWLOC is a theoretical concentration limit of a chemical in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and residential sources. Aggregate risk for piperonyl butoxide exposure is calculated for acute and long-term exposure. Acute and chronic DWLOCs include aggregate exposure from food and drinking water only. The short-term DWLOC aggregates exposures from food, water and residential routes associated with application of piperonyl butoxide and is calculated when there is a common toxicity endpoint for each route of exposure.

The acute DWLOC is $\geq$ 51000 ppb based on the food exposure from the most highly exposed subgroup (children 1-2 years). The chronic DWLOC is $\geq$ 1400 ppb also based on the food exposure for children 1-2 years. The short term DWLOC for children 1-2 years old is 8500 ppb. EFED's model based estimates for peak concentrations of piperonyl butoxide in surface and ground water are 240 and 0.26 ppb respectively; estimates for average surface and ground water concentrations are 60 and 0.26 ppb respectively. Since the model-based estimates for concentrations in surface water and groundwater are well below the calculated acute, short-term, and chronic DWLOCs, HED concludes that aggregate exposure to food and drinking water will not result in an unacceptable risk.

Occupational and Residential Pathway Exposure and Risk

Occupational exposure to piperonyl butoxide can occur from agricultural, pest control, mosquito abatement and veterinary and farm animal applications. Thirty-two exposure scenarios were identified and assessed as representative of occupational exposure for piperonyl butoxide uses. Post-application occupational exposure scenarios are not assessed because there is no endpoint for dermal exposure, the relevant route of exposure for post-application activities. Residential exposure can occur from indoor and outdoor pest control uses and pet application. Fifteen residential handler and post-application exposure scenarios were assessed. Short, intermediate- and long-term MOEs were calculated for this assessment as required based on scenario specific use/exposure patterns.

Exposure data used for the piperonyl butoxide assessment are taken primarily from HED's Standard Operating Procedures for residential and occupational exposure. Risk estimates were conducted using maximum application rates from the Piperonyl Butoxide Master Label. A target Margin of Exposure (MOE) of 300 is considered adequate for short- and intermediate-term occupational and residential exposure via inhalation routes. For long-term occupational inhalation exposures, an adequate target MOE is 1000. The target MOE for residential incidental oral exposures is 100. Exposure estimates indicate MOEs of concern (< the target MOE) at the maximum application rate for ten of the occupational scenarios assessed. The results of the residential exposure assessment indicate that, with one exception, all of residential exposure scenarios assessed result in MOEs greater than the applicable target MOEs and are therefore below the level of concern. The short-term residential bystander inhalation from use of piperonyl butoxide in residential outdoor automatic mister systems is the only scenario with risks of concern. An assessment of residential exposure from use of indoor metered release misters was not conducted due to data limitations. HED recommends that label restrictions provided in the master label be required for indoor automatic mister uses.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The nomenclature and physicochemical properties of piperonyl butoxide are provided in Table 2.

TABLE 2. Piperonyl Butoxide Nomenclature

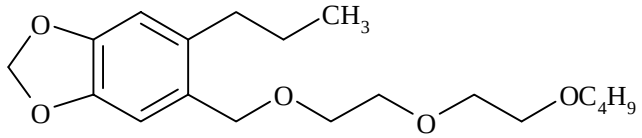
Compound	Chemical Structure
	
Common name	Piperonyl butoxide
IUPAC name	5-[2-(2-butoxyethoxy)ethoxymethyl]-6-propyl-1,3-benzodioxole or 2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether
CAS name	5-[[2-(2-butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxole

TABLE 2. Piperonyl Butoxide Nomenclature	
CAS #	51-03-6

Physicochemical Properties of the Technical Grade of Piperonyl Butoxide		
Parameter	Value	Reference
Boiling point	202-204 °C at 1.9 mm/Hg	D207185, 1/27/99, T. Morton
	180 °C at 1.0 mm/Hg	2002 Farm Chemicals Handbook
Molecular Weight	338.433	2002 Farm Chemicals Handbook
pH	Not applicable because the TGAI has low solubility in water	
Density, bulk density, or specific gravity	1.059 g/mL at 20°C	D172854, 11/30/92, A. Aikens
Water solubility	14.34 μg/mL at 25 °C	RD Memorandum, 12/31/90 (cited under D207185, 1/27/99, T. Morton)
Solvent solubility	Completely miscible (95% solution) in acetone, methanol, petroleum distillate, petroleum ether, methylene chloride, and isooctane	D207185, 1/27/99, T. Morton
Vapor pressure	$<1 \times 10^{-7}$ mm Hg at 25 °C (extrapolated from 1.59×10^{-7} mm Hg at 60 °C	D172854, 11/30/92, A. Aikens
Dissociation constant, pK_a	Not applicable because the TGAI has low solubility in water	
Octanol/water partition coefficient	4.51×10^4	RD Memorandum, 12/31/90 (cited under D207185, 1/27/99, T. Morton)
	$\log K_{ow} = 4.95$	D172854, 11/30/92, A. Aikens
UV/visible absorption spectrum	Not available	

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicity data base for piperonyl butoxide is adequate for the selection of doses and endpoints for use in risk assessment. HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the available studies and established acute and chronic RfDs, as well as doses and endpoints for acute, and short-, intermediate-, and long-term dermal and inhalation exposure scenarios. The Acute RfD is an estimate of a single day oral exposure level for the human population that is likely to be without an appreciable risk of deleterious effects. The chronic RfD is an estimate of a daily oral exposure level that is likely to be without an appreciable risk of deleterious effects during a lifetime. Acute and chronic RfDs are calculated by dividing the No Observable Adverse Effect Level (NOAEL) by the Uncertainty Factors (UF). UFs are used to account for differences between humans (intraspecies variability) and for differences between the test animals and humans (interspecies extrapolation). For occupational and residential exposures, UFs are used to determine adequate margins of exposure (MOEs). The MOE is the ratio of the route appropriate NOAEL to the estimated exposure. The HIARC also evaluated available studies to determine if there was a special sensitivity for infants and children. The toxicological data for piperonyl butoxide are summarized in Tables 3 and 4.

3.1.1 Toxicity Profile

Acute toxicity categories for piperonyl butoxide are shown in Table 3. Table 4 identifies guideline studies and open literature studies conducted for piperonyl butoxide and summarizes their results.

Table 3. Acute Toxicity Data on Piperonyl Butoxide

Study/ Species	MRID	Results	Classification
870.1100 Acute Oral, Rats	41969001	LD_{50} = 4570 mg/kg (m)7220 mg/kg (f)	Category IV (Under Review)
870.1200 Acute Dermal, Rabbits	41969002	LD_{50} = >2000mg/kg	Category IV (Under Review)
870.1300 Acute Inhalation, Rats	41990001	LC_{50} = >5.9 mg/L	Category IV
870.2400 Primary Eye Irritation, Rabbits	41969004	Minimally irritating	Category III (Under Review)
870.2500 Primary Skin Irritation, Rabbits	41969003	Minimally irritating	Category III (Under Review)
870.2600 Dermal Sensitization, Guinea pig	41969005	Negative	Category IV (Under Review)

Table 4. Piperonyl Butoxide Toxicity Study Profile

Developmental/Reproduction Toxicity			
Developmental Toxicity Rat	42380801	Doses: 0, 200, 500 and 1000 mg/kg/day Maternal NOAEL: 200 mg/kg/day Maternal LOAEL: 500 mg/kg/day Reduction in body weight gain and food consumption during 6-15 days of gestation Developmental NOAEL: 500 mg/kg/day (HDT)	Acceptable Guideline
Developmental Toxicity Rabbit	00157157	Doses: 0, 50, 100, and 200 mg/kg/day Maternal NOAEL: 200 mg/kg/day (HDT) Developmental NOAEL: 200 mg/kg/day (HDT)	Acceptable Guideline
2-Gen Reproduction Study Rat	00161118	Doses: 0, 300, 1000 and 5000 ppm 0, 27, 89, 469 mg/kg/day (males) 0, 30, 102, 528 mg/kg/day (females) Parental NOAEL: 89 mg/kg/day Parental LOAEL: 469 mg/kg/day Decreased body weight gain Reproductive NOAEL: 469 mg/kg/day Offspring NOAEL 89 mg/kg/day Offspring LOAEL: 469 mg/kg/day (HDT) Decreased body weight gain in F_1 and F_2 pups	Acceptable Guideline

Table 4. Piperonyl Butoxide Toxicity Study Profile			
Developmental Rats	Kennedy et al., 1977	Doses: 0, 300, 1000 mg/kg/day Maternal NOAEL/LOAEL: 300/1000 mg/kg/day Reduction in mean body weight gain during 6-20 days of gestation Developmental NOAEL 1000 mg/kg/day (HDT)	Non-Guideline
Developmental Rats	Tanaka et al., 1995	Doses: 0, 630, 1065 or 1800 mg/kg/day Maternal NOAEL/LOAEL: 630/1065 mg/kg/day Reduction in bodyweight gain (24-37%) during gestation Developmental NOAEL/LOAEL: 630/1065 mg/kg/day, Limb deformities; HDT had increased resorption rate and decreased number of viable fetuses	Non-Guideline
Developmental Mice	Tanaka et al., 1994	Doses: 0, 1065, 1385, or 1800 mg/kg/day Maternal NOAEL: 1800 mg/kg/day (HDT) Developmental NOAEL/LOAEL: 1065/1385 mg/kg/day: Early and late fetal death and increased resorption rate; HDT had increased incidence of limb deformities	Non-Guideline
Reproduction Single Generation Mice	Tanaka, 1992	Doses: 0,1500, 3000, 6000 ppm Estimated Dose: 0, 225, 450, 900 mg/kg/day Offspring NOAEL/LOAEL: 225/450 mg/kg/day Decreased weight of the pups at postnatal days 7 and 14 Neurobehavioral (Parental) NOAEL/LOAEL: 450/900 mg/kg/day Decreased ambulation and possibly rearing in F_0 male mice at 900 mg/kg/day Neurobehavioral (Offspring) NOAEL/LOAEL: 225/450 mg/kg/day Decreased olfactory orientation in F_1 mice	Non-Guideline
Reproduction Two Generation, Mice	Tanaka et al., 1992	Doses: 0,1000, 2000, 4000, 8000 ppm Chemical intake: 159, 317, 648,1237 mg/kg/day (F_0); 171, 319, 665, 1341 mg/kg/day (F_1) NOAEL/LOAEL (Parental): N/A (No measurements made) NOAEL/LOAEL (Offspring): 319/665 mg/kg/day; Reduction in litter size and litter weight in F_2 generation and decreased weight of the F_1 and F_2 pups during lactation. Neurobehavioral NOAEL/LOAEL (Offspring): 171/319 mg/kg/day. Decreased olfactory orientation in F_2 pups at postnatal day 14	Non-Guideline .
Subchronic Oral Toxicity			

Table 4. Piperonyl Butoxide Toxicity Study Profile			
Subchronic (13 weeks) Rats	Fujitani et al., 1992	Doses: 0, 6000, 12000, or 24000 ppm (diet) Estimated dose 0, 600, 1200, 2400 mg/kg/day NOAEL: <600mg/kg/day LOAEL: 600 mg/kg/day based on 36-39 % increase in relative liver weight and 133-150% increase in gamma glutamyl transpeptidase	Non-Guideline
Subchronic (12 weeks) Rats	Fujitani et al., 1993a	Doses: 0, 6000, 12000, or 24000 ppm (diet) Estimated dose 0, 600, 1200, 2400 mg/kg/day NOAEL: <600mg/kg/day LOAEL: 600 mg/kg/day based on increases in relative liver weight and in gamma glutamyl transpeptidase	Non-Guideline
Subchronic (20 days) Mice	Fujitani et al., 1993b	Doses: 0,1000, 3000 or 9000 ppm (diet) Estimated dose 0, 150, 450, 1350 mg/kg/day NOAEL/LOAEL: 150/450 mg/kg/day based on increased cholesterol, gamma glutamyl transpeptidase and liver weights	Non-Guideline
Subchronic (6 weeks) Mice	Tanaka, 1993	Doses: 0, 1500, 3000 and 6000 ppm Equivalent to 0, 236, 448 and 880 mg/kg/day Neurobehavioral NOAEL:<236 mg/kg/day LOAEL: 236 mg/kg/day based on effects on motor activity-i.e., increased number of turnings and total distance traveled per 10 minutes	Non-Guideline
Chronic Oral Toxicity			
870.4100 Chronic Toxicity -Dogs	42926001, 42926002	Doses: 0, 100, 600 or 2000ppm 0, 2.9, 15.5, 52.8 mg/kg/day (males), 0, 2.8, 16.3, or 71.0 mg/kg/day (females) NOAEL: 15.5 mg/kg/day LOAEL: 52.8 mg/kg/day - Decreased body weight gain, increased in alkaline phosphatase and relative liver weights and hepatocellular hypertrophy (75-100% animals)	Acceptable-Guideline
Combined Chronic Carcinogenicity			
870.4300 Combined chronic toxicity/carcinogenicity Rats	40323701	Doses: 0,30, 100 or 500 mg/kg/day NOAEL: 30 mg/kg/day LOAEL: 100 mg/kg/day -increased liver weight, increased cholesterol levels,gross and histopathological liver effects Negative for liver tumors Note: Butler et al., 1998 confirmed the negative tumor effects after reevaluation of pathological findings	Acceptable/Guideline

Table 4. Piperonyl Butoxide Toxicity Study Profile			
870.4300 Combined chronic toxicity/carcinogenicity Rats	42839601, 42920201	Doses: 0, 547, 1052, 1877 mg/kg/day (males) 0, 537, 1061, and 2002 mg/kg/day (females) NOAEL: <537 mg/kg/day LOAEL: 537 mg/kg/day - Decreased body weight gain, increased liver weights, effect on RBC parameters (abnormal shaped erythrocytes), enlargement and hemorrhage effects in cecum Hepatocellular adenoma and carcinomas in both sexes	Acceptable/ Non-Guideline
870.4300 Combined chronic toxicity/carcinogenicity Mice	42903701, 42978001	Doses: 0, 30, 100 or 300 mg/kg/day NOAEL: 30 mg/kg/day LOAEL: 100 mg/kg/day - Increased liver weight relative to body weight, and liver hypertrophy Hepatocellular adenomas and carcinomas in males and hepatocellular adenomas alone in females Note: Butler et al., 1998 confirmed the negative tumor effects after reevaluation of pathological findings	Acceptable/ Guideline
2-year Carcinogenicity Rats	NTP, 1979	Doses: 0, 5000 and 10,000 ppm (diet) Negative for tumor effects	Non-Guideline
2-year Carcinogenicity Rats	Maekawa et al., 1985	Doses: 0, 5000 and 10,000 ppm (diet) Estimated Chemical Intake: 0, 500 and 1000 mg/kg/day Negative for tumor effects	Non-Guideline
1-year Carcinogenicity Mice	Takahashi et al., 1994	Doses: 0, 6000 and 12,000 ppm (diet) Dose dependent increase in hepatocellular adenomas and carcinomas; Hemangioendothelial sarcomas in males Takahashi et al., 1997reported similar findings in females.	Non-Guideline
11/2 -year Carcinogenicity Mice	NTP, 1979	Doses: 0, 6000 and 12,000 ppm (diet) Negative for tumor effects	Non-Guideline
Subchronic Dermal/Inhalation Toxicity			
21-Day Dermal Toxicity Rabbit	42218201	Doses: 0, 100, 300 and 1000 mg/kg/day Systemic NOAEL: ≥1000 mg/kg/day (HDT) Dermal LOAEL: 100 mg/kg/day (LDT) mild irritant , Very slight erythema, edema and desquamation and histpathological effects such as acanthosis, hyperkeratosis and chronic inflammation of the epidermis	Acceptable/ Guideline

Table 4. Piperonyl Butoxide Toxicity Study Profile			
90-day Inhalation Toxicity Rat	42477101	Doses: 0, 0.015, 0.074, 0.155 and 0.512 mg/L Systemic NOAEL: 0.155 mg/L Systemic LOAEL: 0.512 mg/L increased liver and kidney weights Respiratory NOAEL -Not Established Respiratory LOAEL- 0.015 mg/L (LDT) metaplasia/hyperplasia in the larynx	Acceptable/ Guideline
Metabolism			
Rat Metabolism	41998701 41998401	Most of the administered radioactivity was found in feces and urine in 48 hours after single oral dose of 50 or 500 mg/kg bw. Less than 1.5% of the administered radioactivity was present in tissues after 168 hours. The highest levels were in the small intestine and liver.	Acceptable Guideline
Rat Metabolism	45582701	The dose administration was similar to the metabolism study above. PBO was excreted mainly in 0-48 hour urine and feces and less than 0.5% identified in tissues at 168 hours. Major metabolite in feces was identified as M3 i.e., PBO opened at the methylene dioxy ring (approximately 20% of the radioactivity). Urine contained several radioactive peaks (~20 peaks) and none of these individual peaks exceeded 5% of the administered radioactivity. The urine metabolites are found conjugated with sulfate or glucuronide subsequent to oxidation of PBO in the methylenedioxy ring and/or 2-(2-butoxyethoxy)ethoxymethyl side chain.	Acceptable Guideline
Mutation/Genotoxicity			
870.5100 Bacterial Reverse Mutation Assay	42004502	No evidence of mutagenicity in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 in the presence or absence of metabolic activation Doses 100-5000 µg/plate	Acceptable Guideline
870.5100 Bacterial Reverse Mutation Assay NTP	00143499	No evidence of gene mutations in *Salmonella typhimurium* (TA 1535, TA1537, TA98, TA100) with and without metabolic activation. Dose up to 10 mg/plate	Acceptable Guideline
870.5300 *In vitro* Mammalian Cell Gene Mutation Assay	00147693	Equivocal response in 75 µg/ml only under non-activated conditions in CHO cells. Doses10-100 µg/ml (without activation) Doses 25-500 µg/ml (with activation)	Acceptable Guideline

Table 4. Piperonyl Butoxide Toxicity Study Profile			
870.5375 *In vitro* Mammalian Cell Chromosomal Aberrations Test	43013801	No induction of chromosomal aberration in CHO cells Doses in non activated condition: 15.0-30.0 μg/mL for 10 or 20 hours Doses in S9activated condition:12-120 μg/mL for 2, 10, 20 or 30 hours	Acceptable Guideline
870.5375 *In vitro* Mammalian Cell Chromosomal Aberrations Test NTP	00143499	No evidence of induction of chromosomal aberrations in CHO cells	Acceptable Guideline
870.5550 Unscheduled DNA Synthesis in Rat Primary Hepatocytes	42004503	No evidence of induction of unscheduled DNA synthesis Dose Levels tested: 5,10, 25 and 50 μg/ml Cytotoxic at ≥74.9 μg/ml	Acceptable Guideline
870.5900 *In vitro* Sister Chromatid Exchange Assay NTP	00143499	The study does not indicate sister chromatid exchanges in CHO cells with and without metabolic activation.	Acceptable Guideline
Microsomal Enzyme Inhibition/Others			
In vitro study Liver microsomes Rats, Rabbits, Mice	Franklin, 1972	Inhibition of ethylmorphine N-demethylation by PBO is proportional to amount of Cytochrome P-450 and PBO metabolite complex	Non-Guideline
Regulation of cytochrome P450 enzymes Mice	Adams et al., 1993	Single i.p. dose at 0, 52, 104, 156, 208 or 400 mg PBO/kg bw Induction of cytochrome P450 1a1mRNA, protein and enzyme activity at doses ≥104 mg/kg at 24 hours	Non-Guideline
Regulation of cytochrome P450 enzymes Mice	Ryu et al., 1997	Single i.p. dose at 0, 400 mg PBO/kg bw Induction of cytochrome P450 1a1and 1a2 mRNAs at 24 hours in liver by PBO treatment.	Non-Guideline
WHO Report	JMPR, 1995	PBO Toxicological Evaluation	N/A

3.1.2 Hazard Characterization

Piperonyl butoxide has a low acute toxicity by oral, inhalation and dermal routes. It has been assigned toxicity Category IV by all exposure routes. In the acute studies, piperonyl butoxide has been identified as minimally irritating to eyes and skin. In the subchronic dermal study using rabbits, piperonyl butoxide is classified as a mild irritant. The dermal lesions include gross effects such as very slight erythema, edema and desquamation (30% of the animals) and histopathological effects such as acanthosis, hyperkerartosis and chronic inflammation of epidermis. Piperonyl butoxide is reported negative for dermal sensitization effects. In a

subchronic inhalation toxicity study, mild hyperplasia and metaplasia were noticed in the respiratory tract of rats

The major target organ for piperonyl butoxide induced toxicity is the liver. Subchronic studies in rats showed piperonyl butoxide treatment caused increases in liver weight, and in clinical parameters such as cholesterol and gamma glutamyl transpeptidase activity compared to controls. Liver histopathological effects such as enlargement of hepatocytes with glassy cytoplasm, oval cell proliferation, bile duct hyperplasia, and focal necrosis were observed in treated rats. In ICR mice, similar effects (increased liver weight, cholesterol and gamma glutamyl transpeptidase activity as well as liver histolopathological effects) occurred after 20 days of treatment. One year treatment of dogs with piperonyl butoxide also resulted in pronounced liver effects such as increased liver weight, hepatocyte hypertrophy and elevated serum alkaline phosphatase activity.

In combined chronic/carcinogenic oral toxicity studies, liver tumorigenic effects were reported in rats only when tested at excessive doses. In Fisher 344 rats increases in liver adenomas and carcinomas were reported in both sexes of the rats at doses close to or higher than the limit dose. At these doses, hemorrhage effects in the stomach and cecum were also noticed. No liver tumor effects were reported in Sprague Dawley rats when tested at half limit dose. Maekawa et al. also reported negative carcinogenic effects in F344/DuCrj rats even at doses where high incidence of ileocaecal ulcers were noticed. A 1979 NTP study also reported negative effects for carcinogenicity in same strain of rats. In chronic oral toxicity studies using CD-1 mice, statistically significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas in males and adenomas alone in females (all at $p<0.01$) were reported. The non-guideline studies also reported increased incidences of hepatocellular adenomas and carcinomas and hemangioendothelial sarcoma in CD-1 mice treated with piperonyl butoxide. The NTP study reported negative effects for carcinogenicity in B6C3F1 mice. Piperonyl butoxide is classified as a Group C -possible human carcinogen. No cancer quantification is required for piperonyl butoxide uses.

No developmental toxic effects were noted in guideline studies using rats and rabbits. A few developmental studies in the open literature reported limb deformities, increased resorption and decreased number of viable fetuses in rodents at doses close to or higher than the limit dose. Neurotoxic effects of piperonyl butoxide are not evident from the clinical signs reported in developmental, reproductive and chronic studies submitted to the Agency.

Piperonyl butoxide tested negative in bacterial gene mutation assays. The *in vitro* mammalian cell mutation assays indicate a questionable positive effect for mutation. Piperonyl butoxide tested negative for chromosomal aberration and sister chromatid exchange in CHO cells and no induction of unscheduled DNA synthesis was observed in rat primary hepatocytes.

The main route of phenyl labeled piperonyl butoxide excretion in rats occurs via urine and feces. The amount of administered labeled radioactivity was found at 64-85% in feces, 11-30% in

urine and below 0.5% in tissues. The majority of the administered radioactivity was excreted in 0-48 hour urine and feces. The parent and the M3 metabolite i.e., piperonyl butoxide opened at the methylene dioxy ring were the major compounds identified in feces (approximately 20% of the radioactivity for each). Several radioactive peaks (~20 peaks) were observed in urine samples and none of these individual peaks exceeded 5% of the administered radioactivity. The metabolites in the urine are polar and are found conjugated with sulfate or glucuronide subsequent to oxidation of piperonyl butoxide in the methylenedioxy ring and/or 2-(2-butoxyethoxy)ethoxymethyl side chain.

Piperonyl butoxide is well known to inhibit microsomal enzymes in insects by direct binding to these enzymes and inhibit the breakdown of other insecticides such as pyrethrins and pyrethroids. It also inhibits the microsomal enzymes in several other species (e.g., rats, rabbits, mice). The concentrations at which piperonyl butoxide binds to the enzyme and the affinity of binding to the enzyme and the stability of the cytochrome P450-piperonyl butoxide metabolite complex are some major factors that determine the potency of inhibition among different species.

Piperonyl butoxide is used as a classical compound in several pharmacological experiments to compare the therapeutical or toxicological effects of several drugs before or after metabolism in rodents. Although piperonyl butoxide is reported to inhibit the microsomal enzymes in mammalian system, it is shown to exhibit biphasic effects, i.e., initial inhibition followed by stimulation of microsomal enzymes upon continued exposure. Evidence from the published literature indicates that piperonyl butoxide is administered as a single dose at ≥ 100 mg/kg bw in rats and mice (with the exception of 5-25 mg/kg bw in a couple of mice studies) to inhibit microsomal enzymes. Evidence suggests that the inhibition of microsomal enzymes is a transient effect in these drug interaction studies. As early as 24 hours after the dosing, the increase in microsomal enzymes are observed at the activity level as well as at mRNA and protein levels. The kinetics of the inhibition and/or stimulation and the influence on the specificity of the microsomal enzymes affected upon exposure to piperonyl butoxide are not established in humans.

3.2 FQPA Considerations

HIARC determined that the special FQPA safety factor should be reduced from 10x to 1x due to low degree of concern for the fetal susceptibility effects and no evidence of residual uncertainties for pre- and postnatal toxicity. The FQPA safety factor recommended by the HIARC assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

There are no residual uncertainties identified in the exposure databases relevant to potential exposure to infants and children. The highly refined dietary food exposure assessment uses residue data from the USDA Pesticide Data Program, actual percent crop treated data from BEAD where available, and processing factors from processing study data. The drinking water

assessment utilizes water concentration values generated by model and associated modeling parameters which are designed to provide health protective, high-end estimates of water concentrations which will not likely be exceeded. Use of piperonyl butoxide specific dietary food exposure data is intended to enhance the accuracy of the assessment but will not result in an underestimation of actual exposures/risks. Therefore, these assessments will not underestimate the potential exposure to infants and children resulting from the use of piperonyl butoxide.

3.3 Dose Response Assessment

Doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 5.

Table 5. Endpoints selected by HIARC for Assessing Occupational and Residential Risks for Piperonyl Butoxide

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary General Population	NOAEL= **630** mg/kg/day UF = **100** **Acute RfD** = **6.3** mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **6.3** mg/kg/day	Developmental toxicity study, rats (Tanaka et al., 1995) LOAEL = **1065 mg/kg/day** based on decrease in maternal body weight gain
Acute Dietary Females 13-49 years	N/A	N/A	Acute Dietary Endpoint for General Population is considered protective for this population. No separate endpoint is selected.
Chronic Dietary (All populations)	NOAEL= **15.5** mg/kg/day UF = **100** **Chronic RfD** = **0.16** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.16** mg/kg/day	Chronic oral toxicity study, dogs LOAEL = **52.8** mg/kg/day based on decrease in body weight gain, and increases in alkaline phosphatase activity, liver weight and hepatocellular hypertrophy
Short-Term Incidental Oral (1-30 days)	NOAEL= **89** mg/kg/day	**Residential** MOE = **100** **Occupational** MOE = **100**	Two generation reproduction study, rats LOAEL = **469** mg/kg/day based on the decrease in body weight gain of F_1 and F_2 pups at postnatal day 21
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= **89** mg/kg/day	**Residential** MOE = **100** **Occupational** MOE = **100**	Two generation reproduction study, rats LOAEL = **469** mg/kg/day based on the decrease in body weight gain of F_1 and F_2 pups at postnatal day 21
Short-Term Dermal (1 to 30 days); Intermediate-Term Dermal (1 to 6 months); Long-Term Dermal (>6 months)	N/A	N/A	No systemic, developmental and neurotoxicity concerns at the limit dose. Therefore, no quantification is required. PBO is classified as mild irritant. Contact should be avoided.

Table 5. Endpoints selected by HIARC for Assessing Occupational and Residential Risks for Piperonyl Butoxide			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Inhalation (≤ 2 hrs) (inhalation absorption rate = **100** %)	NOAEL= **630** mg/kg/day	**Residential** MOE = **100**	Developmental toxicity study, rats (Tanaka et al., 1995a) LOAEL = **1065 mg/kg/day** based on decrease in maternal body weight gain
Short-Term Inhalation (1 to 30 days)	Respiratory LOAEL= **3.91** mg/kg/day (0.015 mg/L)	**Residential** MOE = **300** **Occupational** MOE = **300**	Subchronic inhalation toxicity study, rats Respiratory LOAEL = **3.91** mg/kg/day (0.015 mg/L) based on laryngeal hyperplasia and metaplasia
Intermediate-Term Inhalation (1 to 6 months)	Respiratory LOAEL= **3.91** mg/kg/day (0.015 mg/L)	**Residential** MOE = **300** **Occupational** MOE = **300**	Subchronic inhalation toxicity study, rats Respiratory LOAEL = **3.91** mg/kg/day (0.015 mg/L) based on laryngeal hyperplasia and metaplasia
Long-Term Inhalation (>6 months)	Respiratory LOAEL= **3.91** mg/kg/day (0.015 mg/L)	**Residential** MOE = **1000** **Occupational** MOE = **1000**	Subchronic inhalation toxicity study, rats Respiratory LOAEL = **3.91** mg/kg/day (0.015 mg/L) based on laryngeal hyperplasia and metaplasia
Cancer	NA	NA	Classified as "Group C carcinogen" with no quantification

3.3.1 Dietary Exposure Endpoints

3.3.1.1 Acute Reference Dose

For acute dietary general population exposure, an oral NOAEL of 630 was selected from a rat developmental study based on maternal decrease in body weight gain during gestation at the LOAEL of 1065 mg/kg/day. Although the study reported the body weight changes after two gavage doses during gestation days 11-12, it is reasonable to assume that effects could have occurred after a single dose administration and thus are considered appropriate for acute RfD selection. The HIARC recommended a UF of 100x (10x for interspecies and 10x for intraspecies is extrapolation) which results in an RfD of 6.3 mg/kg/day. No separate endpoint was selected for the subpopulation of females, ages 13-49 years, because the study selected for the general population is considered protective for this subpopulation.

Acute RfD (General population) = $\frac{630 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **6.3 mg/kg/day**

3.3.1.2 Chronic Reference Dose

For chronic dietary exposure for all populations, the toxicology endpoint was selected from a chronic oral toxicity study in dogs in which the NOAEL was 15.5 mg/kg/day and the LOAEL was 52.8 mg/kg/day, based on decreases in body weight gain, increased alkaline phosphatase activity and increased liver weight and hepatocellular hypertrophy. This study was selected because; 1) dogs appear to be the more sensitive species for the toxic effects of piperonyl butoxide than rats and mice, 2) it is appropriate for the duration and route of exposure, 3) it has endpoints similar to those reported in other chronic studies such as combined chronic and carcinogenicity studies in mice and rats 4) there are no developmental and reproductive concerns at the doses selected for risk assessment, and 5) it was also used for deriving the Acceptable Daily Intake (ADI) of piperonyl butoxide by the Joint FAO/WHO Meeting on Pesticide Residues in 1995. The HIARC recommended application of a conventional UF of 100 resulting in a chronic RfD of 0.155 mg/kg/day.

$$\textbf{Chronic RfD} = \frac{15.5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.155 mg/kg/day}$$

3.3.2 Occupational and Residential Exposure Endpoints

3.3.2.1 Dermal Exposure

No dose or endpoints were selected for dermal exposure. HIARC concluded that no quantitative dermal assessment is required because no systemic effects were observed at the limit dose in the 21-day dermal toxicity study in rabbits. In the 21-day rabbit dermal toxicity study, dose levels of 1000 mg/kg/day produced no treatment related effect on mortality rate, food consumption, body weight gain, hematology, clinical chemistry, absolute/relative organ weights, and histopathology. However, piperonyl butoxide was observed to be a mild irritant i.e., macro and micropathology of the tested sites exhibited dermal lesions associated with irritation. The dermal lesions include gross effects such as very slight erythema, edema and desquamation (30% of the animals) and histopathological effects such as acanthosis, hyperkeratosis and chronic inflammation of epidermis.

3.3.2.2 Dermal Absorption

Since no dermal endpoint was selected, a dermal absorption factor is not needed.

3.3.2.3 Inhalation Exposure Acute-, Short-, Intermediate-, and Long-Term

For acute inhalation exposure (e.g., < 2 hours) the toxicology endpoint was selected from a rat developmental study in which the oral NOAEL was 630 mg/kg/day based on maternal decrease in body weight gain during gestation at the LOAEL of 1065 mg/kg/day. In the absence of appropriate acute inhalation toxicity studies, the default value of 100% for inhalation

absorption was used for route-to-route extrapolations. The target margin of exposure (MOE) for acute inhalation exposures to piperonyl butoxide is 100 based on the conventional uncertainty factor of 100X.

For short-, intermediate- and long-term inhalation exposures, the toxicology endpoint was selected from a subchronic inhalation toxicity study in rats in which the LOAEL was 3.91 mg/kg/day based on the laryngeal hyperplasia and metaplasia. A respiratory NOAEL was not established because lesions in the larynx were present in all treated groups. The selected endpoint is considered appropriate for assessing all durations of inhalation exposure based on route and duration of the study.

A target MOE of 300 was determined by HIARC to be adequate for short and intermediate term inhalation exposures to piperonyl butoxide. The short- and intermediate-term target MOE includes the conventional uncertainty factor of 100X and an additional 3X uncertainty factor for the use of a LOAEL. For long term exposures, HIARC recommended a target of 1000. HIARC recommended that the long-term target MOE be increased to 1000 to account for lesions in the respiratory tract that might progress into long term adverse effects (e.g., cancer).

3.3.2.4 Incidental Oral Exposure - Short- and Intermediate-Term

For short- and intermediate-term incidental oral exposure, an oral NOAEL of 89 mg/kg/day was selected from a two generation reproduction study in rats based on the decrease in body weight gain of F_1 and F_2 pups at postnatal day 21 at the LOAEL of 469 mg/kg/day. Since the pup weights are affected significantly during lactation phase at postnatal day 21, and there is a trend for decrease in pup weight at postnatal day 4, the endpoints selected are considered appropriate for assessing risks to infants and children from this exposure scenario. A target MOE of 100 was selected as adequate for incidental oral exposures based on the conventional uncertainty factor of 100X.

3.3.2.5 Common Toxicological Endpoints for Aggregate Exposure & Risk

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated if there are common toxicity endpoints (clinical signs) via these routes. However, since the toxicity endpoints selected for oral and inhalation routes of exposure are not common, the risk may not be aggregated for piperonyl butoxide uses.

3.4 Endocrine Disruptor Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) “may

have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP). In the available toxicity studies on piperonyl butoxide, there was no toxicologically significant evidence of endocrine disruptor effects.

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, piperonyl butoxide may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 DIETARY AND DRINKING WATER EXPOSURE/RISK ASSESSMENT

4.1 Summary of Registered Uses

The food/feed uses of piperonyl butoxide which are being supported by the Piperonyl Butoxide Task Force II for reregistration include; preharvest and postharvest uses on agricultural crops, direct and indirect treatments of livestock animals and premises, treatments of commercial and industrial facilities and storage areas where raw and processed food/feed commodities are stored or processed, and mosquito abatement on agricultural fields, including aquatic areas. BEAD provided a screening estimate of usage based on 1997 - 2001 data from OPP's principal agricultural pesticide usage databases. Based on BEAD's estimates the highest usage of piperonyl butoxide is on potatoes (30% crop treated) with all other uses at 5% or less.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

4.2.1.1 Nature of the Residue - Plants and Livestock

Plants

The registrants have submitted acceptable plant metabolism studies on lettuce, cotton, and potatoes. The nature of the residue in plants is adequately understood. The HED Metabolism Assessment Review Committee (MARC) concluded the terminal residues of concern in plants (i.e., residues that need to be regulated or included in the tolerance expression) is piperonyl butoxide *per se)* (T. Morton, D304469, 6/30/04). Metabolism studies conducted on lettuce, cotton, and potato indicated that parent is the only major residue (>10% total radioactive residue (TRR)). However, all the plant metabolism studies are poorly conducted in that only 20 - 40 % of the TRR were successfully identified. Only the lettuce study firmly identified any metabolites. The latter represented conjugates in which the polyether side chain had been hydroxylated or cleaved at one of the ether linkages. These conjugates are similar to some metabolites observed in the rat. MARC does not believe that these metabolites will be significantly more toxic than the parent, but can not exclude them as being significantly less toxic. Since these metabolites were present in lettuce at about the same level as the parent, MARC suggested that the risk assessment team use 2X the parent residue levels for risk assessment, unless field trial data on metabolites on related crops indicate as lower ratio is appropriate. For tolerance expression, parent only is adequate to serve as the misuse indicator.

Piperonyl butoxide is currently exempt from the requirements of tolerances when applied to growing crops in accordance with good agricultural practices (40 CFR §180.1001(b)(4)). Results of studies submitted by the Task Force II on preharvest uses for some crops (based on a reduced number of field trials) show detectable and variable residues of piperonyl butoxide in/on nearly all raw agricultural commodities tested. Therefore, additional residue data reflecting preharvest uses are required for reregistration and tolerance reassessment. When the requested data have been evaluated, HED will recommend revocation of the tolerance exemption in 40 CFR §180.1001(b)(4) along with the establishment of crop group tolerances, if appropriate. The established tolerances for plant commodities, resulting from postharvest uses, are currently expressed in terms of piperonyl butoxide *per se*. Plant tolerances range from 0.25 ppm (potato and sweet potato) to 20 ppm (most cereal grains). The available data are inadequate to support many of the established tolerances resulting from postharvest uses, and additional data are required.

Livestock

The HED MARC concluded the terminal residue of concern in livestock is piperonyl butoxide *per se*. The qualitative nature of the residue in ruminants and poultry, resulting from

dermal treatments, is adequately understood. However, the nature of the residue in ruminants and poultry, resulting from oral treatments, is only partially understood. The oral metabolism studies may be upgraded to acceptable status pending further characterization/identification of radioactive residues in certain matrices/fractions (data are under review) and radiovalidation of the enforcement or data-collection method using samples from either the dermal or oral studies. The metabolism of PBO in lactating goat and hen poultry following dermal administration indicated that parent is the major metabolite (>30% TRR except for goat kidney and liver). There are no specific toxicity concerns for all metabolites, which with few exceptions were present at <10% TRR. Since the major route of exposure would most likely come from dermal treatment of livestock with piperonyl butoxide, MARC concluded that parent only is the residue of toxicological concern to be included in risk assessment and tolerance expression .

Tolerances of 0.25 ppm for milk fat, reflecting negligible residues in milk, and 0.1 ppm for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep have been established. Tolerances of 1 ppm for eggs and 3 ppm for the fat, meat, and meat byproducts of poultry have been established. Additional data are required to reassess the established livestock commodity tolerances and estimate residues from all possible exposure scenarios which include direct application to livestock, premise treatment, and feeding of piperonyl butoxide treated livestock feed.

4.2.1.2 Residue Analytical Method

Plant Commodities

The Pesticide Analytical Manual (PAM) Volume II lists a colorimetric method (Method II) for the enforcement of tolerances for residues of piperonyl butoxide *per se* in/on plant commodities. An improved method, HPLC/fluorescence method has been proposed to replace the existing colorimetric method. The new method can separately determine residues of piperonyl butoxide *per se* and piperonyl butoxide metabolites collectively determined as hydroxymethyl dihydrosafrol (HMDS). The HPLC/fluorescence method has been subjected to a successful independent laboratory validation and has been forwarded to ACL/BEAD for method validation by Agency chemists. The data-collection method used for the analysis of samples, harvested from recent studies pertaining to magnitude of the residue and storage stability studies, was the same HPLC/fluorescence method.

Livestock Commodities

Under Section 180.127, PAM Volume II lists several methods for the enforcement of tolerances for residues of piperonyl butoxide *per se* in animal commodities. The gas liquid chromatography methods (Method I and Methods A and B) are preferred over the colorimetric methods (Methods C and D). Using the GLC methods, residues in samples of milk and tissues are extracted with a mixture of ethyl alcohol, ether, and hexane. Determination is by GLC equipped with flame ionization detector for Methods I and B, and electron capture detector for

Method A. The sensitivity of each method is 0.005 ppm. A new GC/MS method has been proposed for enforcement of piperonyl butoxide tolerances in livestock commodities. The LOQ is 0.01 ppm in milk and eggs and 0.05 ppm in livestock tissue.

4.2.1.3 Multiresidue Methods

According to PAM Volume I, piperonyl butoxide *per se* is completely recovered by multiresidue method Protocols A and D. A recent submission confirms that head lettuce gave acceptable recoveries for piperonyl butoxide *per se* when taken through the complete method in Protocol A using 401E1 + C1 + DL2.

4.2.1.4 Storage Stability Data

Plants

The registrant has submitted the results of several studies which depict the freezer storage stability of piperonyl butoxide in/on oilseeds, nonoily grains, leafy vegetables, root crops and fruits and fruiting vegetables. The available data indicate that fortified residues of piperonyl butoxide *per se* are reasonably stable under frozen storage conditions in some commodities but residues may also decline in some matrices. The Agency will make appropriate adjustments of maximum residues observed in the field trials, if needed, in order to compensate for losses resulting from storage. Storage stability data for piperonyl butoxide *per se* are required for oilseeds, nonoily grains, and root crops. The requested data for oilseeds and root crops should reflect maximum intervals of 30 and 21 months, respectively, and data for nonoily grains should reflect the storage intervals of samples from the outstanding field trials.

Processed Commodities

Data on the storage stability of piperonyl butoxide residues on some processed commodities have been submitted. These data indicate that fortified residues of piperonyl butoxide *per se* are reasonably stable under frozen conditions for up to 12 months in bean cannery waste; tomato juice, puree, and wet and dry tomato pomace; orange juice, dried pulp, and molasses; and cotton meal, soapstock, and crude oil. The available data do not fully support the maximum intervals and conditions of samples from existing tomato, orange, and cotton processing studies. Therefore, additional storage stability data for the processed commodities of oilseeds, grains, and fruits/fruiting vegetables are required. The requested data for the processed commodities of fruits/fruiting vegetables and oilseeds should reflect a maximum interval of 31and 32 months, respectively. The Piperonyl Butoxide Task Force II has indicated that a storage stability study for many processed food/feed items is ongoing.

Livestock Commodities

No storage stability data are available for piperonyl butoxide residues of concern in milk, eggs, and livestock tissues. Therefore, storage stability data as well as information pertaining to the storage conditions and intervals of samples have been requested by HED Storage stability data is required to support the storage intervals and sample conditions from the following submitted studies; feeding studies for dairy cattle and poultry, cattle dermal study, and poultry premise study. For the dairy cattle and poultry oral feeding studies, the data should reflect the actual storage conditions of the samples, and therefore should include frozen storage as tissue/eggs/milk, storage as the dried extract, and storage as the reconstituted extract.

Water

Water storage stability data indicate that fortified residues of piperonyl butoxide are reasonably stable in potable water under frozen storage conditions for up to ~18 months. The collected potable water samples from the submitted field residue trials were stored frozen for ~19-23 months prior to residue analysis. The registrants have indicated that additional fortified potable water samples will be analyzed to encompass the maximum storage interval of samples from the field trials.

4.2.1.5 Magnitude of the Residue in Plants

Overall, the available magnitude of the residue data for supported food/feed commodities are inadequate to support these uses, and therefore, additional data are required for reregistration. The number of trials required to support preharvest uses is listed in the Product and Residue Chemistry assessment (T. Morton, D288366, 6/29/04). Requirements are based on OPPTS 860.1500 GLN for data needed to establish crop group tolerances. Since the bulk of piperonyl butoxide end-use products sold in the market are likely applied to field-growing crops, the majority of the required trials reflect this use pattern. However, HED cannot estimate the residues expected following applications to greenhouses because data are not available. Therefore, the Agency recommends that additional side-by-side trials be conducted to determine the magnitude of residues from applications to greenhouse grown crops (e.g., lettuce, pepper, and tomato). The postharvest uses of piperonyl butoxide on many crop commodities are also not supported by adequate residue data. The Agency prefers that residue data reflecting both preharvest uses and postharvest uses be submitted for crops with both uses.

Piperonyl butoxide is currently exempt from the requirements of tolerances when applied to growing crops in accordance with good agricultural practices (40 CFR §180.1001(b)(4)). When the requested data have been evaluated, HED will recommend revocation of the tolerance exemption and the establishment of crop group tolerances if appropriate.

4.2.1.6 Magnitude of the Residue - Food Handling

Adequate data on the magnitude of residues of piperonyl butoxide *per se* in food-handling establishments and food storage areas are available. These data indicate that the established tolerance of 10 ppm will not be exceeded in representative food commodities and surfaces that had been covered during treatments using representative formulations. The Piperonyl Butoxide Master Label provides adequate instructions for removing or covering food during treatment, and for covering all food processing surfaces treatment and/or thoroughly cleaned surfaces after treatment and before use.

No data are available to support uses of piperonyl butoxide on foods stored in multi-walled paper or cloth bags, and additional data are required for reregistration. The required data should depict the magnitude of residues of concern in representative food types stored in multi-walled paper or cloth bags following surface treatments followed by space treatments followed by bag/container treatments at the maximum use rate for each application type. The bag/container treatments should be in accordance with the conditions and specifications listed in 40 CFR §180.127. Alternatively, the use of piperonyl butoxide on foods stored in multi-walled paper or cloth bags may be removed from all product labels along with the revocation of the associated tolerance.

4.2.1.7 Magnitude of the Residue in Processed Food/Feed

Studies depicting magnitude of the residues of piperonyl butoxide *per se* in the processed commodities of cotton, grape, orange, potato, sugar beet, and tomato are considered adequate pending submission of supporting storage stability data. These studies indicate that piperonyl butoxide may concentrate in certain processed commodities. At this time, HED is unable to recommend appropriate tolerance levels for processed commodities which showed residue concentration because the nature of the residue in plants has not been determined and the highest average field trial residue values for many crop commodities have not been determined. Processing studies for apple, barley, coconut, corn (field), fig, flax, oat, peanut, pineapple, plum, rice, rye, and sorghum are required for reregistration. The required data should depict magnitude of residues of concern in each of the processed commodities for each of these crops. A wheat processing study has been submitted but deemed incomplete because no data were provided for wheat bran, middlings, shorts, and germ. A new wheat processing study is therefore also required for reregistration. The Piperonyl Butoxide Task Force II has indicated that a storage stability study for many processed food/feed items is ongoing.

4.2.1.8 Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

Based upon the initial results of studies depicting the magnitude of the residue in animals and observed residues in feedstuff from preharvest trials, piperonyl butoxide residues of concern are expected to occur in meat, milk, poultry, and eggs. Submitted ruminant studies reflecting dermal and oral treatments have been reviewed and deemed inadequate but upgradeable. The

reviewed studies suggest that the established tolerances for milk and ruminant tissues are too low. A premise spray treatment study with ruminants is also now required for reregistration because the results of the reviewed premise study with poultry suggest that detectable residues at or near the tolerance levels are expected at 1X. Submitted poultry studies reflecting oral and premise spray treatments have been reviewed and deemed inadequate but upgradeable. In addition, a study reflecting dip treatment of piperonyl butoxide on laying hens was reviewed and determined to be inadequate because it does not reflect the supported maximum use rate for direct application to poultry. Therefore, a study reflecting direct applications on poultry using a 10% dust formulation is required for reregistration.

HED would have preferred that the magnitude of the residue study for livestock reflect all possible exposure scenarios which include direct application to livestock, premise treatment, and consumption of treated feed. The Agency will add the residues from all possible exposure routes when the additional requested data have been submitted and reviewed.

4.2.1.9 Magnitude of the Residue in Water, Fish, and Irrigated Crops

Under current policy, EPA is not establishing tolerances for pesticides in potable water and no maximum contaminant level (MCL) for piperonyl butoxide in potable water has been established. The Task Force II has submitted data depicting magnitude of the residue of piperonyl butoxide *per se* in potable water from trials conducted in aquatic environments simulating uses of the pesticide in flooded rice fields. In its review of the study, HED concluded that if the aquatic uses of piperonyl butoxide and pyrethrins are limited to flooded rice fields for the control of adult mosquitos only, then the reregistration requirements for GLN 860.1400 will be considered fulfilled pending label amendments to specify a minimum holding interval or EPA's Office of Water may wish to establish an MCL for piperonyl butoxide in potable water.

4.2.1.10 Confined and Field Accumulation in Rotational Crops

A confined rotational crop study (OPPTS 860.1850) is required to determine the nature and amount of pesticide residue uptake in rotational crops as well as appropriate rotational crop restrictions. A field accumulation study in rotational crops (OPPTS 860.1900) is required if the level of the total radioactive residue in the confined rotational crops is equal to or exceeds 0.01 ppm at the desired rotational interval or at 12 months, whichever is shorter, and once the nature of the residue in the rotational crops is understood.

4.2.1.11 Codex Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of piperonyl butoxide. The Codex MRLs are expressed in terms of Piperonyl butoxide *per se* which is identical to the current U.S. tolerance expression. A numerical comparison of the Codex MRLs and the corresponding current U.S. tolerances for piperonyl

butoxide is presented in the Product and Residue Chemistry assessment (T. Morton, D288366, 6/29/04).

4.2.2 Dietary Exposure/Risk Assessment

4.2.2.1 Consumption Data and Dietary Risk Analysis

Piperonyl butoxide chronic dietary exposure assessments were conducted using two peer reviewed software models, the Lifeline™ model (Version 2.0), and the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03). Both models incorporate consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days.

The Lifeline™ and DEEM™ programs convert raw agricultural commodity (RAC) residues into residues in/on foods as eaten or consumed based on recipes of raw ingredients for each food item. Lifeline™ converts the RAC residues by randomly selecting a RAC residue value from the residue distribution and calculating a net residue for that food based on the ingredients' mass contribution to that food item. Lifeline™ models the individuals's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes and grouping the dairies based on age and the season. This probabilistic methodology is used to estimate both acute and chronic dietary exposures in Lifeline™.

In DEEM™, consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment. DEEM™ estimates chronic dietary exposure by estimating the residue level in each treated food/food form, multiplying that estimate by the average daily consumption estimate for that food/food form, and summing residue intake estimates for all food/food forms to arrive at a total average estimated exposure. For acute exposures DEEM™ uses individual on-day food consumption data on an individual by individual basis. The reported consumption amounts of each food item are matched in multiple random pairings with reside values and them summed in a probabilistic acute dietary exposure assessment.

Both the acute and chronic dietary exposure/risk analyses for piperonyl butoxide were conducted using a highly refined dietary exposure assessment for all supported food uses. USDA Pesticide Data Program (PDP) data were used for commodities which have a preharvest registered uses and for cereal grain crops which have a stored grain use. All other commodities were assigned residues from either the simulated warehouse space spray experiment or the simulated restaurant experiment. Residue data from dermal treatment of livestock studies were used for meat, milk poultry, and eggs because dermal treatment of livestock is the most likely route of exposure for humans. For risk assessment purposes, the terminal residues of concern for plants include the parent and a factor to account for metabolites. Based on recommendations

from the HED MARC, residues were estimated at 2X the parent residue to account for metabolites unless field trial data on metabolites on related crops indicate that a lower ratio is appropriate. For risk assessment purposes, the terminal residue of concern in livestock is piperonyl butoxide, *per se*. Available data from processing studies were used for processed commodities. Percent crop treated (CT) was used for all commodities for which %CT data are available. Where no percent CT data are available, the dietary analyses assumes 100% CT. (T. Morton, 6/30/04, D296887).

4.2.2.2 Acute Dietary Exposure/Risk Assessment

The highly refined probabilistic acute dietary exposure assessment was conducted for all supported piperonyl butoxide food uses and dietary risk estimates are provided for the general U.S. population and various population subgroups. This assessment concludes that for all supported commodities, the acute dietary exposure estimates are below HED's level of concern. The acute dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 20% of the aPAD. Results of the acute dietary exposure analysis are presented in Table 6.

Table 6. Piperonyl Butoxide Acute Dietary (Food) Exposure Estimate and Percent of Acute RfD

Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day) 99.9th percentile		%aPAD 99.9th percentile	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U.S. Population	6.3	0.2825	0.3761	4	6
All Infants (< 1 year old)		0.1550	0.3908	2	6
Children 1-2 years old		0.6473	1.2296	**10**	**20**
Children 3-5 years old		0.4805	0.8027	8	13
Children 6-12 years old		0.3639	0.4112	6	7
Youth 13-19 years old		0.2005	0.3446	3	5
Adults 20-49 years old		0.1772	0.3030	3	5
Adults 50+ years old		0.1818	0.2865	3	5
Females 13-49 years old		0.1768	0.3467	3	6

4.2.2.3 Chronic Dietary Exposure/Risk Assessment

The highly refined chronic dietary exposure assessment was conducted for all supported piperonyl butoxide food uses for the general U.S. population and various population subgroups. This assessment concludes that for all supported commodities, the chronic dietary exposure estimates are below HED's level of concern. The chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 12% of the cPAD. Results of the chronic dietary exposure analysis are presented in Table 7.

Table 7. Piperonyl Butoxide Chronic Dietary (Food) Exposure Estimate and Percent of Chronic RfD					
Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)		%cPAD	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U.S. Population	0.155	0.0078	0.0075	5	5
All Infants (< 1 year old)		0.0034	0.0057	2	4
Children 1-2 years old		0.0182	0.0185	**12**	**12**
Children 3-5 years old		0.0169	0.0163	11	11
Children 6-12 years old		0.0130	0.0117	8	8
Youth 13-19 years old		0.0062	0.0059	4	4
Adults 20-49 years old		0.0063	0.0064	4	4
Adults 50+ years old		0.0060	0.0066	4	4
Females 13-49 years old		0.0063	0.0070	4	5

4.3. Drinking Water Exposure/Risk Pathway

4.3.1. Environmental Fate Assessment

Environmental fate studies indicated that piperonyl butoxide is moderately mobile in soil-water systems. Lab studies indicated that piperonyl butoxide degrades in the environment by photolysis in water (half-life 8.4 hours), and is metabolized by soil microorganisms (half-life 14 days). The aqueous photolysis route may be significant for piperonyl butoxide due to its use in mosquito control applications over intermittently flooded areas. The major degradates of piperonyl butoxide are piperonyl butoxide-alcohol, -aldehyde, and -acid (Attachment 1). These degradates are expected to be more soluble in water and therefore more mobile in soil-water systems than the parent, based on their lower molecular weights and hydrophilic moieties. Based on the structural similarity, HED's MARC believes that these three degradates will likely share the same toxicity as the parent. Therefore, MARC recommended that these three degradates be included in the drinking water assessment. There are no specific toxicity concerns for all other minor metabolites (T. Morton, D304469, 6/30/04).

4.3.2 Estimated Environmental Concentrations

Monitoring data are not available to assess residues of piperonyl butoxide and piperonyl butoxide in drinking water. Therefore, the EFED performed a Tier I drinking water assessment for piperonyl butoxide in surface water and groundwater (W. Eckel, D286223, 5/17/04). EFED used the FIRST model for estimating the upper bound on the concentrations that could occur in surface-water-source drinking water, and the SCI-GROW model to estimate the concentrations in ground water used for drinking water. The drinking water assessment focuses on the terrestrial agricultural uses of piperonyl butoxide since they are considered more likely to contaminate drinking water sources. The cranberry, mosquito adulticide and carp bait uses are not considered, although each has the potential to contaminate water, because EFED does not have standard

methods for estimating drinking water contamination from these use patterns. Estimated drinking water concentrations are presented in Table 8.

Table 8. Drinking Water EDWCs for Piperonyl Butoxide		
Drinking Water Source	**Acute (ug/L)**	**Chronic(ug/L)**
Surface Water	240	60
Groundwater	0.26	0.26

4.3.2.1 Surface Water

The FIRST model was used to estimate environmental concentrations in drinking water from surface water. FIRST is a screening model and produces upper bound values of drinking water concentrations. It is based on a real reservoir in Illinois. It is a single event model which assumes that a single run-off moves a percentage of the applied pesticide into the pond. Input parameters used for the surface water analysis are summarized in Table 9. The peak and mean surface water EDWCs for piperonyl butoxide are 240 and 60 ug/L respectively.

4.3.2.2 Groundwater

EFED used the Screening Concentration in Ground Water (SCI-GROW) model to estimate piperonyl butoxide concentrations in groundwater contaminated by terrestrial uses. SCI-GROW is a regression-based model that uses few input parameters: pesticide's organic carbon partition coefficient (K_{oc}), aerobic soil degradation half-life, and product label application rate and frequency (Barrett, 1997). It provides a groundwater screening concentration for use in determining potential risk to human health from drinking water contaminated with a pesticide. The groundwater concentration is estimated based on the maximum application rates in areas where groundwater is exceptionally vulnerable to contamination. These vulnerable areas are characterized by high rainfall, rapidly permeable soil, and shallow aquifer. Input parameters are summarized in Table 9. The peak and mean groundwater EDWCs for piperonyl butoxide are 0.26 ug/L.

Table 9. FIRST and SCI-GROW Input Parameters for Piperonyl butoxide	
Input Parameter	**Value**
Application Rate	0.5 lb, ten times, at 3-day intervals
Application type	Aerial spray (16% drift) or ground spray (6.4% drift) Unincorporated
Laboratory Soil Metabolism Half-life	73 days (3 x single value of 24.2 days)
Laboratory Aerobic Aquatic Metabolism Half-life	399 days (3 x single values of 133 days)
Laboratory Hydrolysis Half-life (pH 7)	stable
Laboratory Aqueous Photolysis Half-life	5.07 days

Table 9. FIRST and SCI-GROW Input Parameters for Piperonyl butoxide	
Input Parameter	**Value**
Soil-Water Partitioning Coefficient (Koc)	FIRST: 399 (lowest non-sand Koc) SCI-GROW: 599 (median Koc)
Solubility	14.3 ppm (parent)
Percent Cropped Area	87%

5.0 RESIDENTIAL EXPOSURE AND RISK

Based on the Master Label, 14 residential exposure scenarios have been assessed for this RED. Only inhalation and incidental ingestion exposure assessments have been conducted for the residential scenarios. Dermal exposures were not assessed because no dose or endpoints were selected for dermal exposure. Acute, and short- and intermediate-term exposures are expected/assessed for residential exposure scenarios based on use and exposure patterns. Acute exposures are assessed for post-application inhalation exposure to aerial and curbside mosquito abatement applications and for exposures during and after application of aerosol space sprays indoors. Short and intermediate term exposures are assessed for all other handler and post-application exposure scenarios. (B. Daiss, D313107, 8/05; M Crowley, D315334, 8/05)

5.1 Residential Exposure Scenarios

The residential exposure assessment includes three handler and eleven post-application residential exposure scenarios. The term "handler" applies to individuals who mix, load, and apply the pesticide product. The term "post-application" describes individuals who are exposed to pesticides after entering areas previously treated with pesticides. Based on information provided in the Master Label regarding current registrant supported uses, HED assessed the following residential exposure scenarios for the piperonyl butoxide RED.

Application of dust with shaker can, bulb duster, and power duster, a relevant and potentially significant exposure scenario, was not assessed due to lack of dust-specific or adequate surrogate data on inhalation exposure associated with this activity. Additionally, HED did not conduct a quantitative assessment of potential exposure from indoor misters due to data limitations. However, HED recommends that the use restrictions, both general and specific, prescribed by the master label be required for all labels for indoor misters that contain PBO. These restrictions include the following: general use restrictions - do not apply when other persons are present, do not apply when pets (except fish) are present, remove or cover exposed food and wataer before application, remove or cover dishes, utensils, food processing equipment, and food preparation surfaces or wash them thoroughly before use, do not breathe dust, vapors, or spray mist; specific metered release application use restrictions - do not use in nurseries or rooms where infants, ill or aged persons are confined, do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or prepartion areas. It should be noted that a screening assessment of indoor misters was

conducted for the pyrethrin risk assessment. HED believes the pyrethrin assessment provides support for the label restrictions listed above for indoor misters. (T. Dole, D318630, 9/05)

5.1.1 Handler Exposure Scenarios

1) Mixing, loading, and applying liquid spray formulation by low-pressure handwand for indoor surface spray application
2) Mixing, loading, and applying liquid spray formulation by low-pressure handwand for indoor crack and crevice treatment
3) Mixing, loading, and applying liquid spray formulation by hose-end sprayer for lawn and garden application
4) Mixing and loading liquid formulations for the systems' holding tanks for outdoor automatic mister systems

5.1.2 Postapplication Exposure Scenarios

1) Inhalation exposure from application of mosquito adulticide from fixed wing aircraft and/or helicopter
2) Inhalation exposure from application of mosquito adulticide from ULV truck mounted sprayer
3) Toddler incidental ingestion of residue from treated turf grass via hand-to-mouth activities
4) Toddler incidental ingestion of residue via object-to-mouth activity while on treated turf grass
5) Toddler incidental ingestion of soil from treated area
6) Toddler incidental ingestion of residues deposited on carpet via hand-to-mouth activities after use of total release foggers
7) Toddler incidental ingestion of residues deposited on vinyl flooring via hand-to-mouth activities after use of total release foggers
8) Toddler incidental ingestion of residues on pets via hand-to-mouth activities after pet treatment
9) Inhalation exposure to aerosol spray during and after space spray application
10) Bystander acute inhalation exposure during outdoor automatic mister applications
11) Bystander short-term inhalation exposure during outdoor automatic mister applications

5.2 Residential Exposure Data and Assumptions

5.2.1 Application Parameters

Application rates for all of the exposure scenarios assessed are based on information provided in the Piperonyl Butoxide Master Label submitted to the Agency by the Piperonyl Butoxide Task Force II in February 2003. The Master Label provides application parameters including type of application, maximum application rate or concentration, and use restrictions pertinent to human exposure and environmental exposure. The Piperonyl Butoxide Master Label

lists all of the uses that the Piperonyl Butoxide Task Force II members are supporting. Therefore, it is important all labels be revised to reflect the supported uses and maximum allowable application rates provided in the Master Label. For the outdoor automatic mister scenario, the application rate (lb ai/gal soln) used is from a product label assumed to represent typical automatic mister systems.

5.2.2 Handler Exposure Data

It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) or Occupational and Residential Exposure Task Force (ORETF) data to assess handler exposures for regulatory actions when chemical-specific monitoring data or other handler-specific data are not available. PHED was designed by a task force of representatives from the US. EPA, Health Canada, the California Department of Pesticide Regulation, and members of the American Crop Protection Association. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). The ORETF completed four studies which were designed to provide representative surrogate exposure data for pesticide handler risk assessment. The studies monitored professionals applying granular formulation by push spreader and various formulations by pressurized hose-end "handgun" or spray gun; and volunteers representing non-professional consumers applying granular formulation by push spreader and liquid formulations by garden hose-end sprays. Overall, the four ORETF studies were well-conducted and the data for all scenarios is considered of better quality and quantity than what is currently contained in PHED.

Data from the PHED and/or ORETF data bases were used to assess residential handler exposures. Default application assumptions regarding areas treated or amounts applied for residential handler scenarios are documented in the HED Science Advisory Committee on Exposure SOP 12: "Recommended Revisions To The Standard Operating Procedures For Residential Exposure Assessment" (2/22/2001).

5.2.3 Post-application Exposure Data

5.2.3.1 HED Residential Exposure SOPs

The default factors used for the assessment are taken from the Exposure Science Advisory Committee SOP 12. SOP 12 provides values to assess post application inhalation and non-dietary ingestion exposure to lawn care pesticides, and indoor broadcast and crack and crevice treatments.

5.2.3.2 Non-Dietary Exposure Task Force Exposure Data

Primary assumptions for assessing post-application exposure to use of foggers and aerosols in indoor residential settings were based on data provided by the Non-Dietary Exposure Task Force (NDETF). The NDETF was formed in 1996 from members of the Pyrethrin Joint

Venture (PJV) and Piperonyl Butoxide Task Force II, Task Forces set up in the 1980s by producers, formulators, and marketers of the AIs to respond to reregistration needs. NDETF includes; Bayer CropSciences, Botantical Resources Australia, Endura S.p.A, McLaughlin Gormley King Company, Pyrethrum Board of Kenya Prentiss Inc., S.C. Johnson and Son, Inc., and Valent BioSciences Corporation. NDETF's purpose is to produce scientifically sound data on non-dietary exposures to pyrethrin, the pyrethroids, piperonyl butoxide, and MGK-264.

5.2.3.3 Spray Drift Task Force Exposure Data

HED used the AgDRIFT model to calculate airborne concentrations from aerial ULV applications. The model was developed by the Spray Drift Task Force, a coalition of pesticide registrants whose primary objective was to develop a comprehensive data base of off-target spray drift information along with an appropriate modeling system. The model has been peer reviewed by EPA's Science Advisory Panel and has been used in previous mosquito adulticide exposure assessments (e.g. carbaryl, malathion).

5.2.4 Exposure Assumptions

The following assumptions were used in estimating risks from residential exposure to piperonyl butoxide:

- Average body weight of an adult is 70 kg
- Average body weight of an toddler is 15 kg
- Exposure is assessed on day of application (i.e., day zero)
- Exposure duration is short- and intermediate-term unless otherwise indicated (i.e., acute exposures for mosquito and indoor space spray scenarios)
- Maximum application rates as provided by the Piperonyl Butoxide Task Force II were used for all types and methods of application
  For outdoor automatic mister systems, application rates (lb ai/ft^3) from product labels are assumed to represent typical automatic systems
- Maximum daily volumes handled and/or area treated are as follows
  - 0.5 acre is used to represent the surface area treated for broadcast applications to lawns using garden hose-end sprayer;
  - average home treated with space spray or crack and crevice treatment has 1600 square feet of surface area
  - holding tank size for outdoor automatic mister systems is 55 gallons and 250 gallons based on information provided to SRRD from the registrants. It is assumed that a homeowner can prepare the dilute solution and re-fill the holding tank; 1 holding tank is filled per day.
- Mosquito Abatement Scenario
  - for aerial application
    · fixed wing aircraft release height is 100 feet
    · rotary aircraft release height is 30 feet

· average droplet size is 50 microns (per label and/or Public Health Pesticide Applicator Manual (25-50 microns))
· wind speed is 2 mph (per label and/or Applicator Manual (<10 mph))
· temperature is 86° F (per label and/or pesticide Applicator Manual (50-95° F))

- for truck mounted ULV spray application a dilution factor of 0.01 is applied to the airborne concentration at the maximum application rate (i.e., 1% of product released is available for exposure)
- breathing zone airborne concentration is estimated to be approximately 4-6 ft from the ground
- adult breathing rate is 1.0 m^3 per hour; child breathing rate is 0.8 m^3 per hour (NAFTA breathing rates for light activity)
- exposure duration is $\leq$ 2 hours
- exposure is assessed as an acute exposure

• Toddler Outdoor (turf) and Indoor Fogger (carpet and vinyl) Hand to Mouth Scenario
- estimated turf transferable residue is assumed to be 5% of the maximum application rate for sprays
- indoor surface residue is 10 µg/cm^2 based on NDETF study data and a maximum application rate of 0.033 lbs ai/1000 ft^3 for indoor foggers
- hand transfer efficiency is 13% for carpet; 8% for vinyl based on NDETF data
- saliva extraction factor is 50 percent
- surface portion of hand put in mouth is 20 cm^2
- hand-to-mouth exposure frequency is 20 times per hour
- saliva extraction factor is 50 percent
- Exposure duration is 2 hours

• Toddler Object to Mouth Scenario
- object to mouth transfer efficiency is equal to 20% of the application rate
- ingestion rate of residues from mouthing turf or a small object is 25 cm^2

• Toddler Incidental Soil Ingestion Scenario
- soil ingestion rate is 100 mg/day
- fraction of ai available in uppermost cm of soil (fraction/cm) is 100 percent based on soil incorporation into top 1 cm of soil after application

• Toddler Pet Treatment Hand to Mouth Scenario
- one half of a 16 oz spray container is used to treat each animal
- transferable residue from a treated pet is assumed to be 20% of the maximum application rate for sprays
- surface area of a treated (30 lb) dog is 6000 cm^2 (EPA 1993 Wildlife Exposure Factors Handbook - carbaryl)
- saliva extraction factor is 50 percent
- surface portion of hand put in mouth is 20 cm^2
- frequency of hand-to-mouth events is one per day (frequency modified to reflect transferable residue assumption which is based on a 5 minute heavy rubbing/petting technique that would lead to significantly higher hand concentrations than would result from a single contact)

- Inhalation during and after aerosol space spray application
  - ·one 16 oz spray can containing likely maximum of 2.5% ai is used per application ·one application per home
  - adult breathing rate is 1.0 m^3 per hour; child breathing rate is 0.8 m^3 per hour
  - exposure duration is $\leq$2 hours
- Acute inhalation exposure to residential bystanders from outdoor automatic misters
  - all active ingredient is assumed to be "thrown up" in the air immediately and available for exposure (100% active ingredient available) for the entire exposure duration
  - adult breathing rate is 1.0 m^3 per hour; child breathing rate is 0.7 m^3 per hour
  - nozzle height outdoors is assumed to be 8 feet from the ground
  - exposure duration is assumed to be 1 minute per day (0.0167 hours/day) – the entire duration of a nozzle spray
  - exposure is assumed to encompass 1, 1-minute spray event that occurs in the morning or evening (i.e., exposure is to air concentration following 1, 1-minute spray event). Note: this is assumed to be a conservative estimate for acute exposure duration (i.e., labels indicate spray durations may be less – 20-, or 30-seconds)
- Short-term inhalation exposure to residential bystanders from outdoor automatic misters
  - all active ingredient is assumed to be "thrown up" in the air immediately and available for exposure (100% active ingredient available) for the entire exposure duration
  - adult breathing rate is 1.0 m^3 per hour; child breathing rate is 0.7 m^3 per hour
  - nozzle height outdoors is assumed to be 8 feet from the ground
  - exposure duration is assumed to be 5 hours per day for adults and 3 hours per day for toddlers
  - Exposure is assumed to encompass 2, 1-minute, or 2, 30-second spray events that occur in the morning or evening and are also assumed to occur within the 5-hour or 3-hour exposure duration interval (i.e., exposure is to total air concentration following 2, 1-minute, or 2, 30-second spray events)

Non-Standard Exposure Assumptions

Substance and scenario specific data from the NDETF study was used to determine deposition of piperonyl butoxide on vinyl and carpet flooring following use of a total release indoor fogger. Post-fogger release floor concentration was estimated based on data from NDETF Study Volume 2, "Post-Application Deposition Measurements for Pyrethrins & Piperonyl Butoxide Following Use of a Total Release Indoor Fogger". Transfer of piperonyl butoxide from fogger treated carpet was assumed to be 13% of deposition based on data from Volume 29 of the NDETF Study, "Measurement of Transfer of Permethrin and Piperonyl Butoxide Residues from Vinyl and Carpet Flooring Treated with a Fogger Formulation to DSS Wetted Hands Following a Single Hand Press". Indoor air concentration for the period during and after aerosol space spray application was assumed to be 6 mg per cubic meter based on data from Volume 18 of the NDETF Study, "Measurement of Air Concentration , Dermal Exposure, and Deposition of Pyrethrin and Piperonyl Butoxide Following the Use of an Aerosol Spray".

The approach for estimating air concentrations from truck-mounted ULV spray applications is based on a modification of the SOP for residential exposure assessment for inhalation exposure from use of an outdoor space spray for pest control.

Specific reference to "automatic mister systems" is not made in the Piperonyl Butoxide Master Label however there is reference to use of PBO in outdoor domestic sites as a general, crack-and-crevice, or spot surface spray. Four PBO-containing products (EPA Reg. No. 1021-1785, 21165-24,1021-1800, and 655-797) identified in a Consumer Specialty Products Association (CSPA) discussion paper (CSPA, 2005), reference specific nozzle spray systems used in outdoor residential sites. The following is additional general use information from the CSPA discussion paper: holding tanks or reservoirs are typically plastic with 30, 55, or 250 gallon capacity; nozzle height is approximately 8 – 10 feet; nozzle spacing is approximately 10 – 15 feet apart along fences or foliage (i.e., perimeter separation); automatic dispersions are set for 2 to 4 times per day for 30 to 60 seconds per event; systems can be activated manually by homeowners.

5.3 Residential Exposure and Risk Estimates

A target MOE of 100 is considered adequate for acute exposure via inhalation and for short- and intermediate-term incidental ingestion exposures. A target MOE of 300 is considered adequate for short- and intermediate-term inhalation exposures. Mosquito abatement post-application and indoor aerosol space spray application scenarios are assessed as acute exposures. All other residential handler and post-application exposure scenarios are assessed as short- and intermediate-term exposures. Exposure and risk estimates for each scenario are summarized below and a more detailed summary of risk calculations, critical assumptions, and results is provided in Tables 13-21 on pages 53-56 of this document.

The results of the residential exposure assessment indicate that with one exception, all residential exposure scenarios assessed based on master label specified uses result in MOEs greater than the applicable target MOEs i.e., all but one result in exposures below the level of concern. The short-term residential bystander inhalation risk from outdoor automatic misters is the only scenario of concern. Bystander inhalation risk for toddlers is of concern when exposure is to the piperonyl butoxide air concentration resulting from 2, 1-minute spray durations ($MOE_{Toddlers}$ = 190). When exposure is to 2, 30-second spray durations, risk is not of concern ($MOE_{Toddlers}$ = 370).

6.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

The aggregate risk assessment integrates the assessments conducted for dietary, drinking water, and residential exposure. Since there is potential for concurrent exposure via the food, water and residential pathways, the combined exposures are estimated using the methodology described below and are compared with modeling-based estimates of drinking water contamination determined by EFED.

For the aggregate exposure assessment, DWLOCs were calculated and compared with the estimated drinking water concentrations of piperonyl butoxide in ground water and surface water. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that chemical from food, water, and residential sources. The acute and chronic DWLOCs for piperonyl butoxide consider aggregate exposure from food and water only. The short-term DWLOC aggregates exposures from food, water and residential routes associated with application of piperonyl butoxide and is calculated only if there is a common toxicity endpoint for each route of exposure.

6.1 Acute Aggregate Risk Assessment

Acute DWLOCs were calculated based on acute dietary exposure estimates and default body weights and water consumption figures. The Agency's default body weight/water consumption assumptions are 70 kg/2 L (adult male), 60 kg/2 L (youth 13-19 and adult female) and 10 kg/1 L (infants and children <12 years). To calculate the DWLOC, the acute dietary food exposure is subtracted from the aPAD. Acute DWLOCs and EDWCs are provided in Table 10.

Table 10. Piperonyl Butoxide - Drinking Water Levels of Comparison for Acute Dietary Exposure

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day) 99.9th percentile	Acute Water Exposure (mg/kg/day)	DWLOC acute* (ug/L)	Surface Water EDWC (ug/L)	Ground Water EDWC (ug/L)
US Population	6.3	0.38	6	210000	240	0.26
All Infants		0.39	6	59000	240	0.26
Children 1-2		1.23	5	51000	240	0.26
Children 3-5		0.80	5.5	55000	240	0.26
Children 6-12		0.41	6	59000	240	0.26
Youths 13-19		0.35	6	180000	240	0.26
Adults 20-49		0.30	6	210000	240	0.26
Females 13-49		0.35	6	180000	240	0.26
Adults 50+		0.29	6	210000	240	0.26

*$DWLOC_{acute} = \frac{[\text{acute water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg/µg}]}$

where, acute water exposure (mg/kg/day) = [aPAD - (acute food (mg/kg/day)]

The EDWCs for both surface water and groundwater are well below the acute DWLOCs for the general U.S. population and all other population subgroups indicating that acute aggregate exposure to piperonyl butoxide in food and water is less than HED's level of concern for these populations.

6.2 Short-Term Aggregate Risk Assessment

The short term aggregate risk is the estimated risk associated with aggregated risks from

average food exposures, average drinking water exposures, and short-term oral, dermal and inhalation exposures. The toxicity endpoints selected for the dietary, drinking water , and incidental oral routes of exposure may be aggregated because of the common toxicity endpoints (decreased body weight gain) via these routes. Inhalation exposures are not included in the short-term aggregate risk estimate because the toxicity endpoints selected for the chronic dietary/drinking water routes of exposure and those selected for inhalation route of exposure are not based on common effects i.e., the chronic dietary endpoint is based decreased body weight gain and liver effects and the short-term inhalation endpoint is based on laryngeal hyperplasia and metaplasia. The short term aggregate risk for piperonyl butoxide is calculated by adding exposure estimates from dietary, drinking water, and incidental oral exposure pathways for children age 1-2 and comparing them with model based EDWCs determined by EFED. The calculated short-term DWLOC and EDWCs are presented in Table 11.

Table 11. Piperonyl Butoxide - Short-Term Aggregate Risk and DWLOC Calculations

Population	Target Aggregate MOE[1]	MOE food[2]	MOE Incidental Oral[3]	Aggregate MOE (food & residential)[4]	MOE water[5]	Allowable water exposure[6] (mg/kg/day)	Ground Water EDWC (ug/L)	Surface Water EDWC (ug/L)	DWLOC[7] (ug/L)
Child 1-2	100	4800	4700	2400	100	0.85	0.26	60	8500

[1] Target MOE based on UF of 10 for intraspecies variation and 10 for intraspecies extrapolation
[2] MOE food = [(short/ intermediate-term incidental oral NOAEL = 89 mg/kg/day)/(chronic dietary exposure = 0.0185 mg/kg/day)]
[3] MOE incidental oral = [(short or intermediate-term oral NOAEL = 89 mg/kg/day)/(incidental oral residential exposure =0.019 mg/kg/day)];
[4] Aggregate MOE (food and residential) = 1÷ [(1÷MOE food) + (1÷MOE incidental oral)]
[5] Water MOE = 1÷ [(1÷ Target Aggregate MOE) - (1÷Aggregate MOE (food and residential)]
[6] Allowable water exposure = Short or Intermediate Term Oral NOAEL ÷ MOE water
[7] DWLOC (ug/L) = $\frac{\text{allowable water exposure (mg/kg/day) x body weight (kg)}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/ug]}}$ BW = 10 kg, Daily Water Consumption = 1L

EFED's model based estimates for average concentrations of piperonyl butoxide in surface and ground water are 60 and 0.26 ppb respectively. The short term DWLOC for children 1-2 years old is 8500 µg/L. Since the model-based estimates for allowable concentrations in surface water and groundwater are below the calculated short term DWLOC, HED concludes that aggregate exposure to food and drinking water will not result in an unacceptable risk.

6.3 Chronic Aggregate Risk Assessment/DWLOCs

Chronic DWLOCs were calculated based on the chronic dietary exposure estimates and default body weights and water consumption figures. Calculated chronic DWLOCs and EDWCs are provided in Table 11. To calculate the chronic DWLOC, the chronic dietary food exposure is subtracted from the chronic PAD.

Table 12. Drinking Water Levels of Comparison for Chronic Dietary Exposure

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	DWLOC (ug/L)	Surface Water Annual Avg EDWC (ug/L)	Ground Water Annual Avg EDWC (ug/L)
US Population	0.155	0.0078	0.15	5200	60	0.26

Table 12. Drinking Water Levels of Comparison for Chronic Dietary Exposure						
Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	DWLOC (ug/L)	Surface Water Annual Avg EDWC (ug/L)	Ground Water Annual Avg EDWC (ug/L)
All Infants (< 1 year)	0.155	0.0057	0.15	1500	60	0.26
Children 1-2 years	0.155	0.0185	0.14	1400	60	0.26
Children 3-5 years	0.155	0.0169	0.14	1400	60	0.26
Children 6-12 years	0.155	0.0130	0.14	1400	60	0.26
Youth 13-19 years	0.155	0.0062	0.15	4500	60	0.26
Adults 20-49 years	0.155	0.0064	0.15	5200	60	0.26
Females 13-49 years	0.155	0.0070	0.15	4500	60	0.26
Adults 50+	0.155	0.0066	0.15	5200	60	0.26

$$DWLOC_{chronic} = \frac{[\text{chronic water exposure (mg/kg/day)} \times \text{(body weight)}]}{[\text{consumption (L)} \times 10^{-3}\ \text{mg/µg}]}$$

where, chronic water exposure (mg/kg/day) = [cPAD - (chronic food (mg/kg/day)]

The average EDWCs for both surface water (60 ug/L) and groundwater (0.26 ug/L) are less than the chronic DWLOCs, indicating that chronic exposure to piperonyl butoxide in food and water is less than HED's level of concern.

7.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether piperonyl butoxide has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to piperonyl butoxide and any other substances and, piperonyl butoxide does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that piperonyl butoxide has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/fedrgstr/EPA-PEST/2002/January/Day-16/.

8.0 OCCUPATIONAL EXPOSURE AND RISK

Based on the Master Label, 31 occupational exposure scenarios have been assessed for this RED. Only inhalation exposures have been assessed for each of the occupational scenarios. Dermal exposures were not assessed because no dose or endpoints were selected for dermal exposure. Short, intermediate, and long-term exposures are expected/assessed for occupational exposure scenarios based on use patterns. Agricultural handler exposures are assessed as short- and intermediate-term. Pesticide control operator exposures are assessed as short-, intermediate- and long-term. Mosquito abatement exposures are assessed as short- and intermediate-term for aerial and backpack spray applications and short-, intermediate-, and long-term for truck mounted ULV spray applications. (B. Daiss, D313107, 3/xx/04)

8.1 Occupational Exposure Scenarios

Only occupational handler scenarios were assessed for the piperonyl butoxide RED. The term "handler" applies to individuals who mix, load, and apply the pesticide product. Occupational post-application scenarios were not assessed because there is no endpoint for the dermal exposure, the only relevant route of concern for post-application worker exposure. Based primarily on information provided in the Master Label regarding current registrant supported uses, HED assessed the following scenarios for agricultural, professional pest control operator, and mosquito control applications for the piperonyl butoxide RED. Application of dust with shaker can, bulb duster and power duster, a relevant and potentially significant exposure scenario was not assessed due to lack of dust-specific or adequate surrogate data on inhalation exposure associated with this activity.

8.1.1 Agricultural Handler Scenarios

1) mixing and loading liquids for aerial and/or chemigation application to field crops
2) mixing and loading liquids for groundboom application to field crops
3) mixing and loading liquids for airblast application to field crops
4) mixing and loading wettable powders for aerial and/or chemigation application to field crops
5) mixing and loading wettable powders for groundboom application to field crops
6) mixing and loading wettable powders for airblast application to field crops
7) applying liquids aerially to field crops
8) applying liquids with ground boom sprayer to field crops
9) applying liquids with airblast sprayer to field crops
10) mixing, loading and applying liquids with high pressure hand wand for greenhouse application
11) mixing, loading and applying liquids with backpack sprayer or low pressure handwand for greenhouse application
12) mixing loading and applying wettable powder with backpack sprayer or low pressure hand wand for greenhouse application
13) mixing, loading and applying liquids with backpack sprayer or low pressure hand wand for

agricultural premise and equipment application
14) flagging for aerial spray application

8.1.2 Pesticide Control Operator Handler Scenarios

1) mixing, loading and applying liquids indoors for surface spray application with low pressure handwand;
2) mixing, loading and applying liquids indoors for crack and crevice application with low pressure handwand;
3) mixing, loading and applying wettable powders indoors for surface spray application with low pressure handwand;
4) mixing, loading and applying wettable powders indoors for crack and crevice application with low pressure handwand;
5) mixing, loading and applying liquids with backpack sprayer or low pressure hand wand for general outdoor sites;
6) mixing, loading and applying liquids for hand gun sprayer application to lawns;
7) mixing, loading and applying liquids for groundboom application to golf courses
8) mixing, loading and applying liquids for back pack sprayer or low pressure handwand application to stored grain
9) mixing, loading and applying liquids for high pressure handwand application to stored grain
1) mixing, loading and applying liquids for low pressure handwand application to warehouse stored produce
11) applying liquids to golf courses with groundboom sprayer
12) aerosol spray application indoors
13)mixing and loading liquid formulations for the systems' holding tanks for outdoor automatic mister systems

8.1.3 Mosquito Abatement Scenarios

1) mixing, loading liquids for aerial application
2) mixing, loading liquids for ULV truck mounted spray application
3) mixing, loading, applying liquids with truck mounted ULV ground spray (airblast sprayer unit exposure used as surrogate)
4) mixing, loading, applying liquids with back pack sprayer

8.1.4 Direct Application to Pets and Farm Animals (by veterinarians and groomers)

- spray application

8.2 Occupational Exposure Data and Assumptions

8.2.1 Exposure Data

8.2.1.1 Application Parameters

Application rates for all of the occupational exposure scenarios assessed are based on information provided in the Piperonyl Butoxide Master Label which lists all of the uses that Piperonyl Butoxide Task Force II members are supporting. Therefore, it is important all labels be revised to reflect the supported uses and maximum allowable application rates provided in the Master Label.

8.2.1.2 Handler Exposure Data

Data from the PHED or ORETF data bases were used to assess occupational handler exposures. Default application assumptions regarding areas treated or amounts applied for agriculture and mosquito abatement handler exposure scenarios are documented in the HED Science Advisory Committee on Exposure's SOP 9, "Standard Values for Daily Acres Treated in Agriculture" (7/5/2000). Information on how pest control operators use pesticide products was obtained from a survey conducted by the National Pest Management Association (NPMA). NPMA sponsored a "Pest Control Operators (PCO) Product Use and Usage Information Survey".

8.2.2 Exposure Assumptions

The following assumptions were used in estimating risks to occupational handlers from exposure to piperonyl butoxide:

- Average body weight of an adult handler is 70 kg
- Exposure duration is short-term and intermediate term for agricultural handlers and short-, intermediate- and long-term for PCOs and mosquito control applicators
- Baseline inhalation exposure (no respiratory protection)
- Maximum application rates as provided by Piperonyl Butoxide Task Force II were used for all types and methods of application; rates used for exposure assessment are provided in Table 3 of the Occupational Exposure Assessment (B. Daiss, D310033, 11/04)
  Outdoor automatic mister systems - application rate (lb ai/gal soln) used is from a product label assumed to represent typical automatic mister systems (M. Crowley, D315334, 8/05)
- Maximum daily volumes handled and/or area treated used for the scenarios assessed are as follows
  - aerial applications
    · 350 acres per day for typical acreage field crops; 1200 for high acreage field crops (e.g., corn, rice, wheat)
    · 7500 acres per day for mosquito control adulticide applications
  - groundboom applications

· 80 acres treated per day for field crops
· 40 acres treated per day for golf course turf

- airblast applications - 40 acres treated per day for agricultural applications;
- ULV truck mounted sprayer - 3000 acres treated per day for mosquito control (airblast used as surrogate)
- pet groomer/veterinary applications
  · 8 pet animals are treated per day
  · one half of a 16 oz spray container used to treat each animal
- high pressure handwand application - 10 acres treated or 1000 gallons of spray solution used per day
- backpack sprayer or a low pressure handwand sprayer applications
  · 2 acres treated or 40 gallons spray solution used per day for agricultural premise/mosquito control/general outdoor site applications
  · 5 grain storage bins treated per day with cross-sectional area of 1000 square feet per bin
  · 5 food produce storage warehouses treated per day, area treated per warehouse is 10,000 square feet
- pest control operator applications
  · a maximum of 7 commercial buildings or residential homes treated per day for general pest control management activities
  · average area treated per building is 1600 square feet for surface spray and crack and crevice treatment and 12800 cubic feet for space spray application (EPA Exposure Factors Handbook)
  · for outdoor automatic mister systems, holding tank size is 55 gallons and 250 gallons based on information provided to SRRD from the registrants; handlers (i.e., system maintenance workers) are assumed to fill 5 holding tanks per day

Non-Standard Exposure Assumptions

- Assumptions used for veterinary and grain storage treatments are not included in the Occupational Exposure SOPs but represent values that have been used by the Agency in previous assessments (e.g., carbaryl, cyfluthrin).
- Assumptions used for daily area treated for produce storage warehouses are based on best professional judgement.
- Assumptions used for general pest control applicators are based data from the NPMA survey. Based on BEAD's review of the NPMA survey, PCOs conducting general pest control activities would treat an average of between 6 and 7 buildings per day, assuming an 8-hour work day.
- Airblast application unit exposure data was used to assess exposure resulting from truck mounted ULV application of mosquito adulticide. In the absence of more equipment specific data, airblast unit exposure data is thought to provide reasonable surrogate exposure information based on the similarity of the two application methods and has been used for this purpose in previous HED occupational exposure assessments (e.g., carbaryl).

- Specific reference to “automatic mister systems” is not made in the Piperonyl Butoxide Master Label however there is reference to use of PBO in outdoor domestic sites as a general, crack-and-crevice, or spot surface spray. Four PBO-containing products (EPA Reg. No. 1021-1785, 21165-24,1021-1800, and 655-797) identified in a Consumer Specialty Products Association (CSPA) discussion paper (CSPA, 2005), reference specific nozzle spray systems used in outdoor residential sites. The following is additional general use information from the CSPA discussion paper: holding tanks or reservoirs are typically plastic with 30, 55, or 250 gallon capacity; nozzle height is approximately 8 – 10 feet (i.e., off the ground); nozzle spacing is approximately 10 – 15 feet apart along fences or foliage (i.e., perimeter separation); automatic dispersions are set for 2 to 4 times per day for 30 to 60 seconds per event; systems can be activated manually by homeowners.

8.3 Occupational Exposure and Risk Estimates

A target MOE of 300 for the inhalation route is considered adequate for short- and intermediate-term occupational exposure and risk. A target MOE of 1000 is considered adequate for long-term worker exposure via the inhalation route. Agricultural handler exposures are assessed as short- and intermediate- term. Pesticide control operator exposures are assessed as short-, intermediate- and long-term. Mosquito abatement worker exposures are assessed as short- and intermediate-term for aerial and backpack spray applications and short-, intermediate-, and long-term for truck mounted ULV spray applications. Exposure and risk estimates for each scenario are summarized below and a more detailed summary of exposure and risk calculations, critical assumptions, and results is provided in Tables 22-26 on pages 56-61 of this document.

The results of the worker exposure assessment indicate that the following agricultural application exposure scenarios result in MOEs less than the target MOE of 300 for inhalation for short- and intermediate-term exposure.

- Mixing and loading wettable powders for aerial and/or chemigation application to field crops. The MOE at the maximum application rate of 0.5 lb ai/acre for typical acreage field crops is s 40; the MOE for high acreage field crops is 11. MOEs greater than the target MOE of 300 result at an application rate of 0.06 lb ai/acre for the typical acreage field crop scenario and 0.018 lb ai/acre for the high acreage scenario.

- Mixing and loading wettable powders for groundboom application to field crops. The MOE at the maximum application rate of 0.5 lb ai/acre is 160. MOEs greater than the target MOE of 300 MOEs result at an application rate of 0.25 lb ai/acre for this scenario.

- Mixing, loading and applying liquids for high pressure handwand application to greenhouse crops. The MOE at the maximum application rate of 1.5 lb ai/acre is 160. MOEs greater than the target MOE of 300 result at an application rate of 0.7 lb ai/acre for this scenario.

- Mixing, loading and applying wettable powders for low pressure handwand application to greenhouse crops. The MOE at the maximum application rate of 1.5 lb ai/acre is 85. MOEs greater than the target MOE of 300 result at an application rate of 0.4 lb ai/acre for this scenario.

The results of the worker exposure assessment indicate that the following pest control operator application exposure scenarios result in MOEs less than the target MOE of 1000 for long-term exposure.

- Mixing, loading and applying liquids for low pressure handwand application for crack and crevice treatment. The MOE at the maximum application rate of 2.2 lb ai/1000 ft^2 and 7 buildings treated per day is 380. MOEs greater than the target MOE of 1000 result at the maximum application rate of 2.2 lb ai/1000 ft^2 if the number of buildings treated per day is reduced to one, or if the application rate is reduced to 0.3 ai/1000 ft^2 for 7 buildings treated per day.

- Mixing, loading and applying wettable powders for low pressure handwand application for indoor surface spray treatment. The MOE at the maximum application rate of 0.56 lb ai/1000 ft^2 and 7 buildings treated per day is 40. MOEs greater than the target MOE of 1000 result if the application rate is reduced to of 0.16 lb ai/1000 ft^2 and only 1 building is treated per day.

- Mixing, loading and applying wettable powders for low pressure handwand application for crack and crevice treatment. The MOE at the maximum application rate of 2.2 lb ai/1000 ft^2 and 7 buildings treated per day is 10. MOEs greater than the target MOE of 1000 result if the application rate is reduced to of 0.16 lb ai/1000 ft^2 and only 1 building is treated per day.

- Applying aerosols for indoor space spray application. The MOE at the likely maximum application rate of 0.025 lb ai per 16 oz. can with two cans applied per building and 7 buildings treated per day is 615. MOEs greater than the target MOE of 1000 result if the application rate is reduced to 0.012 lb ai per 16 oz can.

The results of the worker exposure assessment indicate that the following mosquito abatement application exposure scenario results in an MOE less than the target MOE of 1000 for long-term exposure.

- Mixing and loading liquids for aerial spray application. The MOE at the maximum application rate of 0.08 lb ai/acre is 390 if an open cab is assumed. MOEs greater than the target MOE of 1000 result if the maximum application rate is reduced to 0.03 0.08 lb ai/acre.

- Mixing, loading and applying liquids for ULV truck mounted spray application. The MOE at the maximum application rate of 0.08 lb ai/acre is 260 if an open cab is assumed. MOEs greater than the target MOE of 1000 result at the maximum application rate if a closed cab is assumed.

All other occupational exposure scenarios assessed based on master label specified uses result in MOEs greater than the applicable target MOEs.

9.0 INCIDENT REPORT

Based on data from Poison Control Centers, there appears to be a greater risk of moderate or major symptoms among those exposed to products containing pyrethrins and piperonyl butoxide than those exposed to pyrethrins alone. A detailed review of symptoms found that respiratory symptoms (bronchospasm, cough/choke, and dyspnea) and selected dermal symptoms (dermal irritation/pain, itching, and rash) were more likely if the exposure included piperonyl butoxide. These symptoms are likely the reason for increased risk of moderate effects which typically would require medical attention. Other literature suggests that pyrethrin-based products may pose a hazard to asthmatics. The findings from analysis of symptoms from Poison Control Centers suggests that piperonyl butoxide adds to that risk.

Based on these findings, it is recommended that labeling advise handlers using products containing piperonyl butoxide as follows: Avoid contact with skin or eyes. Susceptible individuals may experience irritant or allergic-type reactions. Persons with respiratory illness may experience difficulty breathing and should avoid use in enclosed spaces and consult their physician prior to use. (Review of Pyrethrins Incident Reports - Second Revision, J. Blondell, D320300, 8/16/04)

10.0 UNCERTAINTIES AND RISK CHARACTERIZATION

The dietary exposure analyses conservatively assume use of maximum application rates. The highly refined acute and chronic dietary exposure assessment for piperonyl butoxide could be refined further by additional residue data on the level of metabolites and parent in cereal grains and beans/peas where the ratio of 2 as recommended by the HED MARC was used. In addition, monitoring data or field trial residues for field corn, sweet corn, and cottonseed could further refine the assessment.

The drinking water assessment focuses on the terrestrial agricultural uses of piperonyl butoxide since they are considered more likely to contaminate drinking water sources. The cranberry, mosquito adulticide and carp bait uses are not considered, although each has the potential to contaminate water, because EFED does not have standard methods for estimating drinking water contamination from these use patterns.

Inhalation risk estimates are conservatively based on a local or portal of entry effect (i.e., laryngeal hyperplasia and metaplasia). The NOAEL for systemic inhalation effects is 30 times higher than the endpoint selected based on local effects.

Initial exposure estimates for the occupational and residential assessment are conservatively based use of maximum application rates provided in the master label. It was also assumed, based on the master label, that products for all applications are supported/available in multiple forms i.e.,

liquids, dust, wettable powders. However, given that the majority of piperonyl butoxide products are available as liquid formulations, scenarios involving handling and application of liquid formulations are likely to be more representative of actual exposure.

The SOP default occupational and residential unit exposures selected for each scenario were based on central-tendency values from PHED. The mean exposure data from the NDETF study used to estimate exposures from indoor fogger release is comprehensive and should accurately represent likely exposures from total release foggers.

Uncertainties identified by BEAD regarding the NPMA survey data used to determine potential exposures to PCOs should also be noted. Regarding the robustness and validity of the NPMA survey data BEAD drew the following conclusions. Given that there are approximately 19,000 PCO firms in the U.S., it is highly unlikely that a sample size of 67 represents a statistically valid sample. The use of a retrospective survey methodology may have introduced errors in the data. Pesticide survey firms like Doane use a prospective survey instrument sent to growers in advance thus allowing them to keep detailed accounts of their pesticide usage in real time throughout the year. Despite its small size and retrospective methodology, however, the information collected is more robust than BEAD typically gets when asking questions of this nature. BEAD typically contacts 1-5 PCO's and asks chemical specific questions which may bias the responses if PCO's value the chemical under review. (D. Brassard, D305276, 7/04) HED believes the NPMA survey provides reasonable estimates of average number of buildings treated per day by PCOs.

For pest control operator and mosquito abatement scenarios, assuming full day, long term application for each application method may significantly overestimate total exposure. Based on data on usage of likely piperonyl butoxide containing pesticides presented in the NPMA survey, this assumption would result in significant overestimate of exposure for PCOs. Similarly, assuming continuous usage of piperonyl butoxide containing pesticides for mosquito abatement applications would also significantly overestimate total exposure based on personal communication with mosquito control district officials regarding current usage of these products. However, piperonyl butoxide is used to control a large number and a wide variety of pests and labels do not restrict or preclude repeated applications or long term use. Given the potential for multiple applications and long-term use for occupational handlers, inclusion of a repeated use/long-term exposure scenario for pest control operators and mosquito abatement is considered reasonable.

Application of dust with shaker can, bulb duster and power duster, a relevant and potentially significant exposure scenario for both residential and occupational exposures, was not assessed due to lack of dust-specific or adequate surrogate data on inhalation exposure associated with this activity. Use of existing applicator data for surrogate exposure assumptions for this exposure scenario would likely underestimate potential risk

HED did not conduct a quantitative assessment of potential exposure from indoor misters due to data limitations. However, HED recommends that the use restrictions, both general and

specific, prescribed by the master label be required for all labels for indoor misters that contain PBO. These restrictions include the following: general use restrictions - do not apply when other persons are present, do not apply when pets (except fish) are present, remove or cover exposed food and water before application, remove or cover dishes, utensils, food processing equipment, and food preparation surfaces or wash them thoroughly before use, do not breathe dust, vapors, or spray mist; specific metered release application use restrictions - do not use in nurseries or rooms where infants, ill or aged persons are confined, do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or prepartion areas. It should be noted that a screening assessment of indoor misters was conducted for the pyrethrin risk assessment. HED believes the pyrethrin assessment provides support for the label restrictions listed above for indoor misters.

For outdoor automatic misters, the exposure durations used in the short-term inhalation exposure (5 hours/day for adults, 3 hours/day for toddlers) represent the 95th percentile values for time spent outdoors at a restaurant/picnic area (USEPA, 1997). During this exposure period the individual is assumed to be exposed to the average air concentration following 2 spray events each lasting a period of either 1 minute or 30 seconds. Inhalation risks of concern are seen when exposure results from air concentrations after 2, 1-minute spray durations. Although this spray duration is considered reasonable, lower spray durations (i.e., 20- or 30-second durations) may be more representative of actual system rates. Standard label language for use rates could provide a more refined risk assessment. Label language requiring systems to activate at times when people are not present (i.e., EPA Reg. No. 1021-1785) or systems with motion detectors would also significantly reduce inhalation exposure. Risks were calculated based on automatic dispersions (i.e., 2-6 pre-set spray events per day) throughout the day. It was noted in the CSPA discussion paper that the systems can be manually activated by the homeowner. Although costs of re-filling and service maintenance costs would likely deter homeowners from frequent or over-use, label language indicating appropriate daily spray cycles should be considered.

11.0 DATA NEEDS

11.1 Product Chemistry Data Requirements

Outstanding product chemistry data requirements for piperonyl butoxide Technical Grade Active Ingredients are listed for each individual registrant in Table 1 of the Product and Residue Chemistry Document (T. Morton, D288366, 6/30/04). In addition, the Agency requires that the registrants of all products listed in Table 1 submit updated Confidential Statements of Formulation for all basic and alternate formulations on which the name of the producer or producers and the site(s) where the piperonyl butoxide TGAIs are produced are clearly identified.

11.2 Residue Chemistry Data Requirements

- Label revisions and clarifications are required for some crops in order to reflect the use pattern parameters for which adequate residue data are available.

- Further analytical work to upgrade the previously submitted oral metabolism studies with ruminant and poultry. Representative egg, milk, and tissue samples from the dermal or oral ruminant/poultry metabolism studies must be analyzed using the enforcement method or any preferred data-collection method to determine whether the method(s) adequately recover Piperonyl butoxide residues of concern. Data are under review.

- Additional storage stability data for plant (and processed) and livestock commodities to upgrade previously submitted studies or to support new studies.

- Data to support uses of piperonyl butoxide on foods stored in multi-walled paper or cloth bags.

- A magnitude of the residue study with ruminants reflecting premise treatment. In addition, the registrants need to perform further analysis on milk samples from the dermal and oral studies.

- A magnitude of the residue study with poultry reflecting direct applications to laying hens using a 10% dust formulation.

- Magnitude of the residue studies reflecting preharvest uses on representative commodities of all crop groups (and a few miscellaneous commodities) which are being supported for reregistration.

- Magnitude of the residue studies reflecting postharvest uses for all crops (except potato and sweet potato) which are being supported for reregistration

- Processing studies on apple, barley, coconut, corn (field), fig, flax, oat, peanut, pineapple, plum, potato, rice, rye, sorghum, and wheat.

- A confined rotational crop study. A field accumulation study in rotational crops (OPPTS 860.1900) is required if the level of the total radioactive residue in the confined rotational crops is equal to or exceeds 0.01 ppm at the desired rotational interval or at 12 months, and once the nature of the residue in the rotational crops is understood.

Tables 13-21 - Residential Exposure and Risk Estimates

Table 13. Piperonyl Butoxide Inhalation Exposure & MOEs for Residential Handler Activities Target Short and Intermediate Term MOE = 300						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Crop[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (1)	30	Indoor Residential Surface Spray	0.56 lb ai per 1000 ft^2	1 home of avg area of 1600 sf	0.0004	10400
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (2)	30	Indoor Residential Crack & Crevice	2.2 lb ai per 1000 ft^2	1 home of avg area of 1600 sf	0.0015	2700
Mixing/Loading/Applying Liquids for Garden hose-end sprayer application (3)	11	Lawn	1 lb ai per acre	0.5 Acres per day	0.000079	51000

[1]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Crops and use patterns are from the master label
[3]Application rates are based on maximum values provided in the master label Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = short-term and intermediate-term endpoint for inhalation; 4 mg/kg/day (inhalation LOAEL)/ Daily Inhalation Dose. Target Short and Intermediate Term Inhalation MOE is 300. Target Long Term Inhalation MOE is 1000.

Table 14. Piperonyl Butoxide Inhalation Exposure & MOEs for Residential Handler Activities for Outdoor Automatic Mister (4)					
Application Rate (lb PBO/gal)	Reservoir size (gallons)	System Maintenance (tanks filled/day)	Daily Dose (mg/kg/day)	Acute (Target MOE = 100)	ST/IT (Target MOE = 300)
0.0384	55	1	0.0000362	17000000	110000
	250	1	0.0001645	3800000	24000

[1] Daily Dose (mg/kg/day) = [Application Rate (lb PBO/gal soln) * Unit Exposure (1.2 ug/lb PBO handled) * Holding Tank Size (gallons/tank) * System Maint. (tanks/day) * Inhalation Abs. Factor (100%)] / [CF (1000 ug/mg) * Body Weight (70 kg)]
[2] MOE = Acute NOAEL (630 mg/kg/day) / Daily Dose (mg/kg/day) or ST/IT LOAEL (3.91 mg/kg/day) / Daily Dose (mg/kg/day)

Table 15. Piperonyl Butoxide Post-application Inhalation Risks To Adults and Children Following Mosquito Adulticide Application - Acute Target MOE = 100				
Exposed Individual	Breathing Zone Concentration (mg/m^3)	Breathing Rate (m^3/hr)	Inhalation Dose (mg/kg/day)[1]	MOE
Aerial Spray (Fixed Wing and Rotary Aircraft) (1)				
Adult	0.03	1.0	0.0009	740000
Child	0.03	0.8	0.004	160000
Truck Mounted ULV Sprayer (2)				
Adult	0.3	1.0	0.005	75000

Table 15. Piperonyl Butoxide Post-application Inhalation Risks To Adults and Children Following Mosquito Adulticide Application - Acute Target MOE = 100				
Exposed Individual	Breathing Zone Concentration (mg/m^3)	Breathing Rate (m^3/hr)	Inhalation Dose (mg/kg/day)[1]	MOE
Child	0.3	0.8	0014	20000

ID (mg/kg/day) = Inhalation Dose = PDR/ BW

$PDR_{(t)}$ (mg/day) = $((AR_t)$ (lb ai/A)-BZC * BR * ED

where:

PDR = Potential Dose Rate - inhalation dose in breathing zone after spray application (mg/m^3)

AR = application rate lb/ai per acre converted to mg/m^3

BZC = Breathing Zone Concentration (mg/m^3) - from Ag Drift Model for aerial spray application; 1% of application rate for truck mounted ULV sprayer application

BR = Breathing rate for adult or child (m^3/hr) (1.0 m^3/hr adult, 0.8 m^3/hr child)

BW = 70 kg for adult; 15 kg for toddler

ED = Exposure Duration (2 hr/day)

MOE = Acute Inhalation NOAEL (630 mg/kg/day)/Inhalation Dose (mg/kg/day) MOEs are reported to two significant figures.

Table 16. Piperonyl Butoxide Post-application Incidental Ingestion Risks to Toddlers Reentering Treated Lawns Hand to Mouth (HTM), Object to Mouth (OTM), Incidental Soil Ingestion (SI), Aggregate - Short-Term Target MOE = 100										
Inputs	Hand to Mouth (3)			Object to Mouth (4)			Soil Ingestion (5)			Aggregate
Max App Rate (lb ai/A)	Hand Transfer (ug/cm^2)	Daily Oral Dose (mg/kg/day)	MOE	Dislogeable Foliar Residue (ug/cm^2)	Daily Oral Dose (m/k/d)	MOE[3]	Soil Residue (ug/g)	Daily Oral Dose (m/k/d)	MOE	Aggregate MOE
1.0	0.56	0.015	6000	2.2	0.004	24000	0.00075	0.00005	>1E+06	4800

1 DOD(mg/kg/day) = Daily Oral Dose (PDR/ BW)

BW = 15 kg for toddler

Hand To Mouth Calculation

$PDR_{(t)}$ (mg/day) = $(HTF_{(t)}$ ($\mu g/cm^2$) * SEF * SA * Freq * ED/1000 (µg/mg)

where:

PDR = Potential Dose Rate at time (t) attributable for activity in a previously treated area (mg/day)

$HTE_{(t)}$ = Hand Transfer Efficiency at time t = 5% of Application Rate ($\mu g/cm^2$)

SEF = Saliva Extraction Factor (50%)

SA = Surface Area of Two Fingers ($20\ cm^2$)

Freq = Frequency of Hand to Mouth Events (20)

ED = Exposure Duration in hours (2 hr/day)

t = Postapplication Day on which exposure is being assessed (day 0)

MOE = Short Term Oral NOAEL (89 mg/kg/day)/Daily Oral Dose (mg/kg/day)

Object to Mouth Calculation

$PDR_{(t)}$ (mg/day) = $(DFR_{(t)}$ ($\mu g/cm^2$) * SA/1000 (µg/mg)

where:

PDR = Potential Dose Rate at time (t) attributable for activity in a previously treated area (mg/day)

$DFR_{(t)}$= Dislogeable Foliar Residue at time t = 20% of Application Rate ($\mu g/cm^2$)

SA = Surface Area of grass or toy mouthed by toddler ($25\ cm^2$ day)

t = Postapplication day on which exposure is being assessed (day 0)

MOE = Short Term Oral NOAEL (25 mg/kg/day)/[Daily Oral Dose (mg/kg/day) MOEs are reported to two significant figures

Soil Ingestion Calculation

$PDR_{(t)}$ (mg/day) = $(SR_t$ * IgR * CF1)

where:

PDR = Potential Dose Rate - nondietary ingestion rate from contact with treated surface (mg/day)

SR_t = Soil Residue on day "t" (µg/g)

IgR = Ingestion Rate of soil (mg/day); (100 mg/day)

CF1 = Weight unit conversion factor (1E-6 g/µg)

where:

SR_t = Application Rate ($\mu g/cm^2$) * 1/cm * 0.67 cm^3/g soil [1/cm is fraction of ai available in uppermost cm of soil]

t = Postapplication Day on which exposure is being assessed, assumed to be day zero

MOE = Short Term Oral NOAEL (25 mg/kg/day)/[Daily Oral Dose (mg/kg/day) MOEs are reported to two significant figures

AggMOE=1/(1/MOE HTM + 1/MOE OTM + 1/MOE SI)

Table 17. Piperonyl Butoxide Post-application Incidental Ingestion Risks To Toddlers Playing on Vinyl Floor and Carpet after Treatment with Fogger Formulation - Short-Term Target MOE = 100				
Indoor Surface	Indoor Surface Residue (ug/cm^2)	Hand Transfer Efficiency (%)	Daily Oral Dose (mg/kg/day)[1]	MOE
carpet (6)	10	13	0.021	4200
vinyl (7)	10	8	0.035	2600

1 DOD(mg/kg/day) = Daily Oral Dose = PDR/ BW

$PDR_{(t)}$ (mg/day) = $(ISR_{t)}$ (µg/cm^2) * TE * SEF * SA * Freq * ED/1000 (µg/mg)

where:

PDR = Potential Dose Rate on day of application (mg/day)
ISR = Indoor Surface Residue (µg/cm^2) at maximum AR of 0.033 lbs ai/1000 ft^2
HTE = Hand Transfer Efficiency - transfer of (13% for carpet; 8% for vinyl)
SEF = Saliva Extraction Factor (50%)
SA = Surface Area of Two Fingers (20 cm^2)
Freq = Frequency of Hand to Mouth Events (20)
ED = Exposure Duration in hours = 2 hr/day
t = Postapplication Day on which exposure is being assessed (day 0)
BW = 15 kg for toddler
MOE = Short Term Oral NOAEL (89 mg/kg/day)/Daily Oral Dose (mg/kg/day) MOEs are reported to two significant figures.

Table 18. Piperonyl Butoxide Post-application Incidental Ingestion Risks To Toddlers Playing with Pets after Treatment with Spray Formulation - Short-Term Target MOE = 100				
Application Method	AR (mg ai/cm^2)	Transferable Residue (%)	Daily Oral Dose (mg/kg/day)[1]	MOE
Aerosol Spray (8)	1.14	20	0.15	600

1 DOD(mg/kg/day) = Daily Oral Dose = PDR/ BW

$PDR_{(t)}$ (mg/day) = $((AR_{t)}$ (mg ai/animal) * F)/SA_{pet}) * SEF * SA_{hands} * Freq

where:

PDR = Potential Dose Rate - nondietary ingestion dose from contact with treated pets (mg/day)
AR = Application Rate or amount applied to animal in a single treatment (mg ai/animal) = ½ of 16 oz spray container with maximum of 3% ai per 6000 cm^2/animal
F_{AR} = Fraction of Application Rate available for dermal contact as transferable residue (20%)
SA_{pet} = Surface Area of a treated dog (6000 cm^2/animal)
t = Time After Application (0 days)
SEF = Saliva Extraction Factor (50%)
SA_{hands}= Surface Area of the hands (20 cm^2)
Freq = Hand-to-Mouth Events (1 event/day)
BW = 15 kg for toddler
MOE = Short Term Oral NOAEL (89 mg/kg/day)/Daily Oral Dose (mg/kg/day) MOEs are reported to two significant figures.

Table 19. Piperonyl Butoxide Inhalation Risks To Adults and Children During and After Indoor Space Spray Application - Acute Target MOE = 100					
Application Method	Exposed Individual	Breathing Zone Concentration (mg/m^3)	Breathing Rate (m^3/hr)	Inhalation Dose (mg/kg/day)[1]	MOE
Aerosol Spray (9)	Adult	5.8	1.0	0.09	3800
	Child	5.8	0.8	0.28	1000

Inhalation Dose (mg/kg/day) = PDR/ BW

$PDR_{(t)}$ (mg/day) = $((AR_{t)}$ (lb ai/A)- BZC * BR * ED

where:

PDR = Potential Dose Rate - inhalation dose in breathing zone after spray application (mg/m^3)
AR = application rate - 1 16 oz can containing 2.5% ai applied to a 16 x 16 x 8 ft room
BZC = Breathing Zone Concentration (mg/m^3) - measured air concentration from NDETF study adjusted to reflect a likely maximum application rate
BR = Breathing rate for adult or child (m^3/hr) (1.0 m^3/hr adult, 0.8 m^3/hr child)
BW = 70 kg for adult; 15 kg for toddler
ED = Exposure Duration (2 hr/day)34

MOE = Acute Inhalation NOAEL (630 mg/kg/day)/Inhalation Dose (mg/kg/day) MOEs are reported to two significant figures.

Table 20. Outdoor Automatic Mister Residential Outdoor Bystander – Acute Inhalation Exposure and Risk Estimates (10)

Population Sub-Group	Application Rate (lb PBO/ft^3-min)	Air Concentration[1] (mg PBO/m^3)	Inhalation Rate (m^3/hour)	Daily Dose[2] (mg/kg/day)	MOE[3] (Target MOE = 100)
Adult	0.000000469	7.50974	1	0.00179	350000
Toddler	0.000000469	7.50974	0.7	0.00585	110000

[1] Air Concentration (mg PBO/m^3) = Application Rate (lb PBO/ft^3-min) * CF (454000 mg/lb) * CF (35 ft^3/m^3) * # Spray Events (1) * Spray Duration (1 minute)
[2] Daily Dose (mg/kg/day) = [Air Concentration (mg PBO/m^3) * Inhalation Rate (m^3/hr) * Inhalation Abs. Factor (100%) * Exposure Duration (0.0167 hrs/day)] / Body Weight (kg)
[3] MOE = Acute NOAEL (630 mg/kg/day) / Daily Dose (mg/kg/day)

Table 21. Outdoor Automatic Mister Residential Outdoor Bystander – Short-Term Inhalation Exposure and Risk Estimates (11)

Population Sub-Group	Application Rate (lb PBO/ft^3-min)	Inhalation Rate (m^3/hour)	Spray Duration (minutes)	Air Concentration[1] (mg PBO/m^3)	Daily Dose[2] (mg/kg/day)	MOE[3] (Target MOE =300)
Adult	0.000000469	1	1	0.150195	0.010728	360
			0.5	0.0750974	0.005364	730
Toddler	0.000000469	0.7	1	0.150195	0.0210273	**190**
			0.5	0.0750974	0.0105136	370

[1] Air Concentration (mg PBO/m^3) = [Application Rate (lb PBO/ft^3-min) * CF (454000 mg/lb) * CF (35 ft^3/m^3) * # Spray Events (2) * Spray Duration (min)]/Dilution Factor (100)
[2] Daily Dose (mg/kg/day) = [Air Concentration (mg PBO/m^3) * Exposure Duration (hrs/day) * Inhalation Rate (m^3/hr) * Inhalation Abs. Factor (100%)]/ Body Weight (kg)
[3] MOE = ST/IT NOAEL (3.91 mg/kg/day) / Daily Dose (mg/kg/day)

Tables 19-23 – Occupational Exposure and Risk Estimates

Table 22. Piperonyl Butoxide Inhalation Exposure & MOEs for Agricultural Handler Activities Target Short and Intermediate Term MOE = 300

Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)[1]	Crop[2]	Application Rate[3]	Daily Area Treated[4]	Inhalation Dose (mg/kg/day)[5]	Inhalation MOE[6]
Mixer/Loader						
Mixing/Loading Liquids for Aerial and/or Chemigation application (1)	1.2	Field Crops	0.50 lb ai/acre	350 Acres/day	0.003	1300
		High Acre Crops		1200 A/day	0.01	380
Mixing/Loading Liquids for Groundboom application (2)	1.2	Field Crops	0.5 lb ai/acre	80 Acres/day	0.00069	5800
Mixing/Loading Liquids for Airblast application (3)	1.2	Field Crops	0.5 lb ai per acre	40 Acres/day	0.00021	19000
Mixing/Loading Wettable Powders for Aerial application and/or Chemigation application (4)	43	Field Crops	**0.50** lb ai/acre	350 Acres/day	0.11	**40**
			0.06 lb ai/acre		0.013	310
		High Acre Crops	**0.50** lb ai/acre	1200 Acres/day	0.37	**11**
			0.018 lb ai/acre		0.013	300

Table 22. Piperonyl Butoxide Inhalation Exposure & MOEs for Agricultural Handler Activities Target Short and Intermediate Term MOE = 300						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Crop[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Mixing/Loading Wettable Powders for Groundboom application (5)	43	Field Crops	**0.50** lb ai/acre	80 Acres/day	0.025	**160**
			0.25 lb ai/acre		0.012	325
Mixing/Loading Wettable Powders for Airblast application (6)	43	Field Crops	0.50 lb ai/acre	40 Acres/day	0.012	330
Applicator						
Sprays for Aerial application (7)	0.07	Field Crops	0.50 lb ai/acre	350 Acres/day	0.00018	23000
Sprays for Groundboom applic (8)	0.74	Field Crops	0.50 lb ai/acre	80 Acres/day	0.00042	9500
Sprays for Airblast application (9)	4.5	Field Crops	0.50 lb ai/acre	40 Acres/day	0.0013	3100
Mixer/Loader/Applicator						
Mixing/Loading/Applying Liquids for High-Pressure Handwand application (10)	120	Greenhouse	**1.5** lb ai/acre	10 Acres/day	0.026	**160**
			0.07 lb ai/acre		0.012	330
Mixing/Loading/Applying Liquids for Low Pressure Handwand or Backpack Sprayer application (11)	30	Greenhouse	1.5 lb ai/acre	2 Acres/day	0.0013	3100
Mixing/Loading/Applying Wettable Powders for Low-Pressure Handwand or Backpack Sprayer application (12)	1100	Greenhouse	**1.5** lb ai/acre	2 Acres/day	0.05	**85**
			0.4 lb ai/acre		0.013	320
Mixing/Loading/Applying Liquids for Low Pressure Handwand or Backpack Sprayer application (13)	30	Outdoor Premise & Equipment	1 lb lb ai/acre	2 Acres/day	0.0009	4700
Flagger						
Flagging for Spray application (14)	0.35	Field Crops	0.5 lb ai per acre	350 Acres per day	0.00088	4600

[1]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Crops and use patterns are from the master label
[3]Application rates are based on maximum values provided in the master label Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = short-term and intermediate-term endpoint for inhalation; 4 mg/kg/day (inhalation LOAEL)/ Daily Inhalation Dose. Target Short and Intermediate Term Inhalation MOE is 300. Target Long Term Inhalation MOE is 1000.

Table 23 Piperonyl Butoxide Inhalation Exposure & MOEs for Residential Handler Activities for Outdoor Automatic Mister (4)					
Application Rate (lb PBO/gal)	Reservoir size (gallons)	System Maintenance (tanks filled/day)	Daily Dose[1] (mg/kg/day)	Acute (Target MOE = 100)	ST/IT (Target MOE = 300)

0.0384	55	5	0.0002534	3500000	22000
	250	5	0.0011516	770000	4800

[1] Daily Dose (mg/kg/day) = [Application Rate (lb PBO/gal soln) * Unit Exposure (1.2 ug/lb PBO handled) * Holding Tank Size (gallons/tank) * System Maint. (tanks/day) * Inhalation Abs. Factor (100%)] / [CF (1000 ug/mg) * Body Weight (70 kg)]
[2] MOE = Acute NOAEL (630 mg/kg/day) / Daily Dose (mg/kg/day) or ST/IT LOAEL (3.91 mg/kg/day) / Daily Dose (mg/kg/day)

Table 24. Piperonyl Butoxide Inhalation Exposure & MOEs for Pesticide Control Operator Activities Target Short and Intermediate Term MOE = 300 Target Long Term MOE = 1000

Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)[1]	Use[2]	Application Rate[3]	Daily Area Treated[4]	Inhalation Dose (mg/kg/day)[5]	Inhalation MOE[6]
Mixer/Loader/Applicator						
Mixing/Loading/Applying Liquids for Low Pressure Handwand application -Surface Spray (1)	30	Indoor Surface Spray	0.56 lb ai per 1000 sf	7 buildings avg area treated - 1600 sf	0.0034	1500
Mixing/Loading/Applying Liquids for Low Pressure Handwand application - Crack & Crevice Treatment (2)	30	Indoor Crack & Crevice	2.2 lb ai per 1000 sf	**7** buildings avg area treated - 1600 sf	0.12	**380**
				1 building avg area treated - 1600 sf	0.0004	2700
Mixing/Loading/Applying Wet Powders for Low Pressure Handwand application - Surface Spray (3)	1100	Indoor Surface Spray	**0.56** lb ai per 1000 sf	**7** buildings avg area treated -1600 sf	0.113	**40**
				1 building avg area treated - 1600 sf	0.0015	**280**
			0.16 lb ai per 1000 sf	**1** building avg area treated - 1600 sf	0.004	1020
Mixing/Loading/Applying Wettable Powders for Low Pressure Handwand application - Crack & Crevice Treatment (4)	1100	Indoor Crack & Crevice	**2.2** lb ai per 1000 ft^2	**7** buildings avg area treated - 1600 sf	0.385	**10**
				1 building avg area treated - 1600 sf	0.055	**70**
			0.16 lb ai per 1000 ft^2	**1** building avg area treated - 1600 sf	0.004	1020
Mixing/Loading/Applying Liquids for Low Pressure Handwand and Backpack Sprayer application (5)	30	Outdoor Premise	3.5 lb ai per acre	2 acres per day	0.003	1300
Mixing/Loading/Applying Liquids for Handgun (lawn) Sprayer application (6)	1.8	Lawn Care	1 lb ai per acre	5 Acres per day	0.00013	31000
Mixing/Loading Liquids for Groundboom application (7)	1.2	Golf course	1 lb ai per acre	40 Acres per day	0.0007	5800
Mixing/Loading/Applying Liquids for Low Pressure Handwand and Backpack Sprayer application (8)	30	Stored Grain	0.5 lb ai per 1000 ft^2	5 bins per day 1000 ft2 per bin	0.0011	3700

Table 24. Piperonyl Butoxide Inhalation Exposure & MOEs for Pesticide Control Operator Activities Target Short and Intermediate Term MOE = 300 Target Long Term MOE = 1000						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Use[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Mixing/Loading/Applying Liquids for High-Pressure Handwand application (9)	120	Stored Grain	0.5 lb ai per 1000 ft^2	5 bins per day 1000 ft2 per bin	0.0043	930
Mixing/Loading/Applying Liquids for Low-Pressure Handwand application (10)	30	Stored Produce	0.1 lb ai per 1000 ft^2	5 storage facilities per day 10000 ft2 per facility	0.0021	1900
Applicator						
Sprays for Groundboom application (11)	0.74	Golf course	1 lb ai per acre	40 Acres per day	0.0004	9500
Sprays for Aerosol Application (12)	1300	Indoor Space Spray	**0.025** lb ai per 16 oz can	7 homes per day 2 cans per home	0.0065	**615**
			0.012 lb ai per 16 oz can		0.0033	1200

[1]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2] Use patterns are from the master label
[3]Application rates are based on maximum values provided in the master label Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = short-term and intermediate-term endpoint for inhalation; 4 mg/kg/day (inhalation LOAEL)/ Daily Inhalation Dose. Target Short and Intermediate Term Inhalation MOE is 300. Target Long Term Inhalation MOE is 1000.

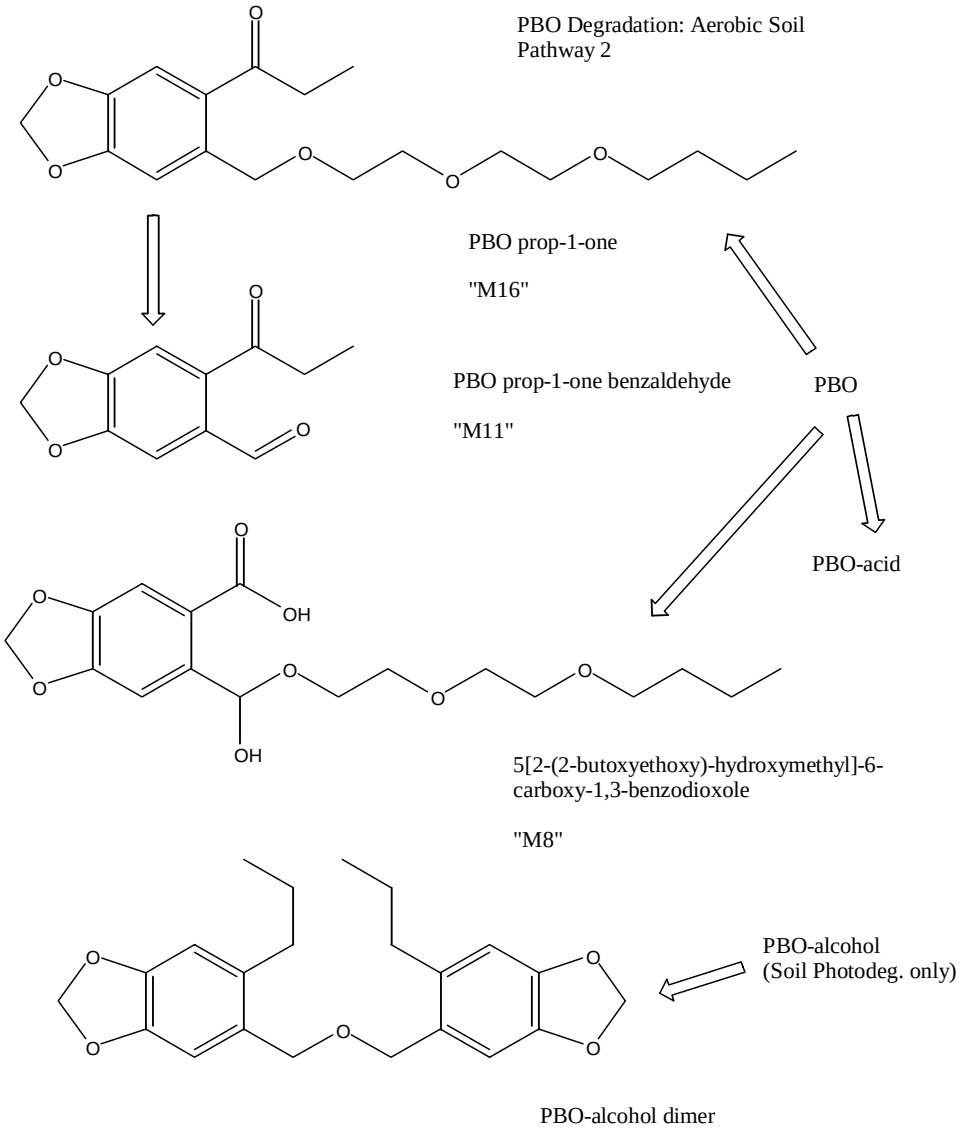
Table 25. Piperonyl Butoxide Inhalation Exposure & MOEs for Mosquito Abatement Activities Target Short and Intermediate Term MOE = 300 Target Long Term MOE = 1000						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Use[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Mixer/Loader						
Mixing/Loading Liquids for Aerial application (1)	1.2	Mosquito Control	**0.08** lb ai per acre	7500 Acres per day	0.0100	**390**
			0.03 lb ai per acre		0.0040	1000
Mixing/Loading Liquids for ULV truck mounted spray application (2)	1.2	Mosquito Control	0.08 lb ai per acre	3000 Acres per day	0.0041	970
Mixer/Loader/Applicator						
Sprays for ULV truck mounted spray (Airblast Surrogate Unit Exposure) (3)	4.5 **(Open Cab**)	Mosquito control	0.08 lb ai per acre	3000 Acres per day	0.0150	**260**
	0.45 **(Closed Cab)**				0.0004	2600

Table 25. Piperonyl Butoxide Inhalation Exposure & MOEs for Mosquito Abatement Activities Target Short and Intermediate Term MOE = 300 Target Long Term MOE = 1000						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Use[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Mixing/Loading/Applying Liquids for Backpack sprayer application (4)	30	Mosquito Control	0.08 lb ai per acre	2 acres per day	0.00007	58000

[1]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Use patterns are from the master label
[3]Application rates are based on maximum values provided in the master label. Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = short-term and intermediate-term endpoint for inhalation; 4 mg/kg/day (inhalation LOAEL)/ Daily Inhalation Dose. Target Short and Intermediate Term Inhalation MOE is 300. Target Long Term Inhalation MOE is 1000.

Table 26. Piperonyl Butoxide Inhalation Exposure & MOEs for Pet Groomer and Veterinarian Activities Target Short and Intermediate Term MOE = 300 Long-Term MOE =1000						
Exposure Scenario	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Use[2]**	**Application Rate[3]**	**Daily Area Treated[4]**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE[6]**
Aerosol Application	1300	Pet Spray	0.03 lb ai per 16 oz can	8 pets treated per day ½ can of spray per pet	0.002	1800

[1]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2] Use pattern is from the master label
[3]Application rates are based on maximum values provided in the master label
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = short-term and intermediate-term endpoint for inhalation; 4 mg/kg/day (inhalation LOAEL)/ Daily Inhalation Dose. Target Short and Intermediate Term Inhalation MOE is 300. Target Long Term Inhalation MOE is 1000.


PBO Degradation: Aerobic Soil
Pathway 2
PBO prop-1-one
"M16"
PBO prop-1-one benzaldehyde
"M11"
PBO
PBO-acid
5[2-(2-butoxyethoxy)-hydroxymethyl]-6-carboxy-1,3-benzodioxole
"M8"
PBO-alcohol
(Soil Photodeg. only)
PBO-alcohol dimer